9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

9.1 Treat most adults with type 1 diabetes with continuous subcutaneous insulin infusion or multiple daily doses of prandial (injected or inhaled) and basal insulin. **A**

9.2 For most adults with type 1 diabetes, insulin analogs (or inhaled insulin) are preferred over injectable human insulins to minimize hypoglycemia risk. **A**

9.3 Early use of continuous glucose monitoring is recommended for adults with type 1 diabetes to improve glycemic outcomes and quality of life and to minimize hypoglycemia. **B**

9.4 Automated insulin delivery systems should be offered to all adults with type 1 diabetes. **A**

9.5 To improve glycemic outcomes and quality of life and to minimize hypoglycemia risk, most adults with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake and fat and protein intake. They should also be taught how to modify the insulin dose (correction dose) based on concurrent glycemia, glycemic trends (if available), sick-day management, and anticipated physical activity. **B**

9.6 Insulin treatment plan and insulin-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted to incorporate specific factors that impact choice of treatment and ensure achievement of individualized glycemic goals. **E**

Insulin Therapy

Insulin treatment is essential for individuals with type 1 diabetes because the hallmark of type 1 diabetes is absent or near-absent β-cell function. In addition to hyperglycemia,

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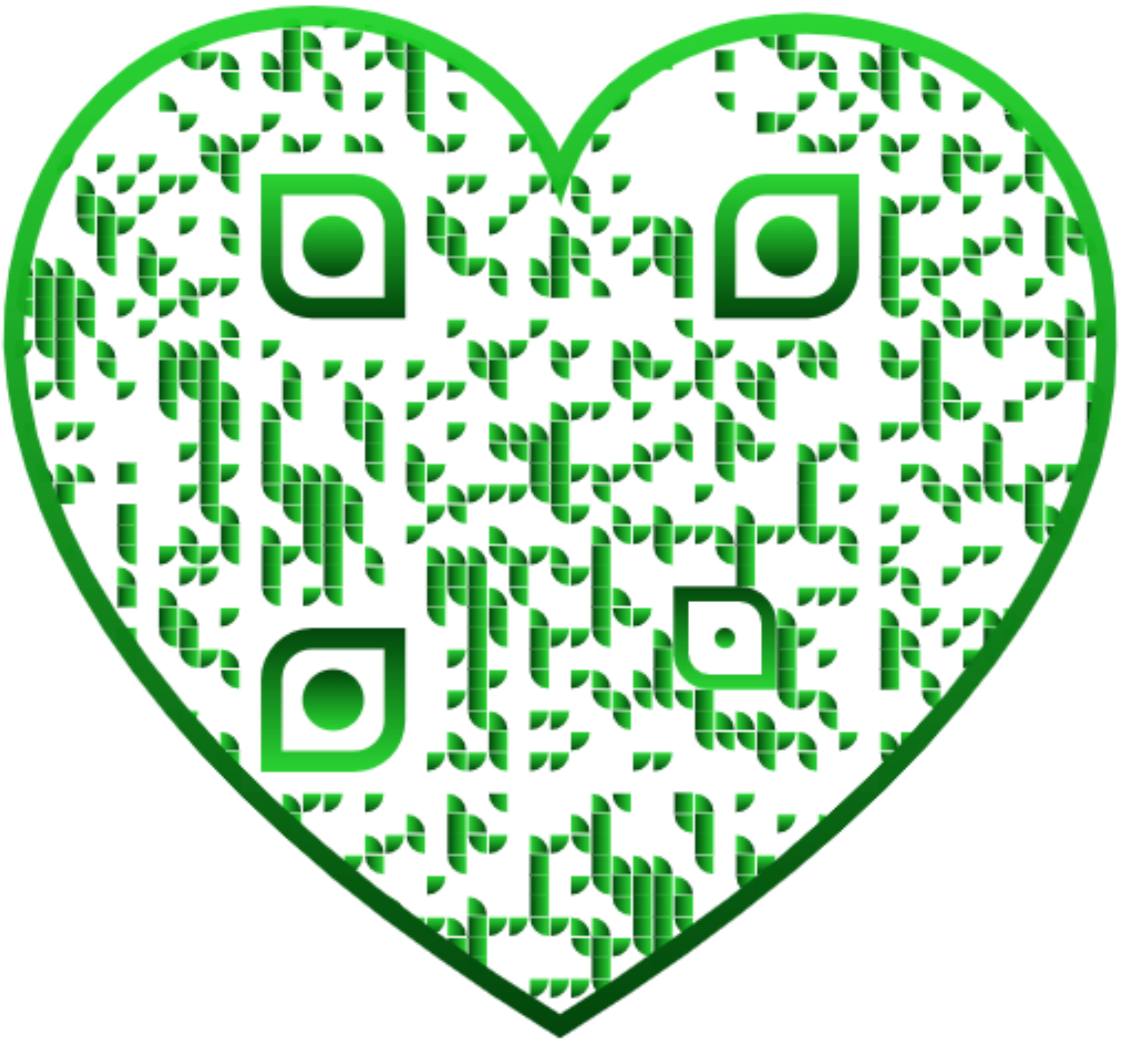

insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily insulin injections for the six or seven decades after the discovery of insulin. Over the past four decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3). The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive management (7%) led to ∼50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 person-years of therapy) (1). Follow-up of participants from the DCCT demonstrated fewer macrovascular and microvascular complications in the group that received intensive treatment. Achieving intensive glycemic goals during the active treatment period of the study had a persistent beneficial impact over the 20 years after the active treatment component of the study ended (1–3).

Insulin replacement plans typically consist of basal insulin, mealtime insulin, and correction insulin (**Fig. 9.1**) (4). Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant and consistent plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain and lower A1C compared with injectable human insulins (5–7). Two injectable ultra-rapid-acting analog (URAA) insulin formulations are available that contain excipients that accelerate absorption and provide more activity in the first portion of their profile compared with the other RAA (8,9). Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA (10) (see also subsection ALTERNATIVE INSULIN ROUTES IN PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES). These newer formulations may cause less hypoglycemia while improving postprandial glucose excursions and administration flexibility (in relation to prandial intake) compared with RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14).

Despite the advantages of insulin analogs in individuals with type 1 diabetes, the expense and/or complexity of treatment required for their use may be prohibitive (**Table 9.1**). There are multiple approaches to insulin treatment. The central precept in the management of type 1 diabetes is that some form of insulin be given in a defined treatment plan tailored to the individual to prevent diabetic ketoacidosis (DKA) and minimize clinically relevant hypoglycemia while achieving the individual's glycemic goals. The impact of the introduction of interchangeable biosimilars and unbranded versions of some analog products as well as current and upcoming price reductions on insulin access need to be evaluated. Reassessment of insulin-taking behavior and adjustment of treatment plans to account for specific factors, including cost, that impact choice of treatment is recommended at regular intervals (every 3–6 months).

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. A systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (15). Use of CSII is associated with improvement in quality of life, particularly in areas related to fear of hypoglycemia and diabetes distress, compared with multiple

Representative relative attributes of insulin delivery approaches in people with type 1 diabetes

Injected insulin plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	$$$
Less-preferred, alternative injected insulin plans			
MDI with NPH + RAA or URAA	++	++	$$
MDI with NPH + short-acting (regular) insulin	++	+	$
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	$

Continuous insulin infusion plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
Automated insulin delivery systems	+++++	+++++	$$$$$
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	$$$$$
Insulin pump therapy without automation	+++	+++	$$$$

Figure 9.1—Choices of insulin plans in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. The number of plus or dollar signs is an estimate of relative association of the plan with greater flexibility, lower risk of hypoglycemia, and higher costs between the different plans. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Adapted from Holt et al. (4).

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Table 9.1—Examples of subcutaneous insulin treatment plans

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Plans that more closely mimic normal insulin secretion				
Insulin pump therapy (also including AID systems: hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 30–50% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with premeal insulin ∼15 min before eating.	Can adjust basal rates for varying insulin sensitivity by time of day, for exercise, and for sick days. Flexibility in meal timing and content. Pump can deliver insulin in increments of fractions of units. Potential for integration with CGM for AID systems. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive plan. Must continuously wear one or more devices. Risk of rapid development of ketosis or DKA with interruption of insulin delivery. Potential reactions to adhesives and site infections. Most technically complex approach (harder for people with lower numeracy or literacy skills).	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. Basal rates: adjust based on overnight, fasting or daytime glucose outside of activity of URAA/RAA bolus. AID systems: carbohydrate ratio, insulin on board, targets, and/or ISF may be adjusted, depending on the system. Make sure to review and adjust manual mode settings, if available.
MDI: LAA + flexible doses of URAA or RAA at meals	LAA once daily (insulin detemir or insulin glargine may require twice-daily dosing); generally 30–50% of TDD. Mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose.	Can use pens for all components. Flexibility in meal timing and content. Insulin analogs cause less hypoglycemia than human insulins.	At least four daily injections. Most costly insulins. Smallest increment of insulin is 1 unit (0.5 unit with some pens). LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. LAA: based on overnight or fasting glucose or daytime glucose outside of activity time course, or URAA or RAA injections.
MDI plans with less flexibility				
Four injections daily with fixed doses of N and RAA	Pre-breakfast: RAA ∼20% of TDD. Pre-lunch: RAA ∼10% of TDD. Pre-dinner: RAA ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

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Table 9.1—Continued

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Four injections daily with fixed doses of N and R	Pre-breakfast: R ∼20% of TDD. Pre-lunch: R ∼10% of TDD. Pre-dinner: R ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. R can be dosed based on ICR and correction. All meals have R coverage. Least expensive insulins.	Greater risk of nocturnal hypoglycemia with N. Greater risk of delayed post-meal hypoglycemia with R. Requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.	Pre-breakfast R: based on BGM after breakfast or before lunch. Pre-lunch R: based on BGM after lunch or before dinner. Pre-dinner R: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.
Plans with fewer daily injections				
Three injections daily: N + R or N + RAA	Pre-breakfast: N ∼40% TDD + R or RAA ∼15% TDD. Pre-dinner: R or RAA ∼15% TDD. Bedtime: N ∼30% TDD.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injection in middle of day. Morning N covers lunch to some extent. Same advantages of RAAs over R. Least (N + R) or less expensive insulins than MDI with analogs.	Greater risk of nocturnal hypoglycemia with N than LAAs. Greater risk of delayed post-meal hypoglycemia with R than RAAs. Requires relatively consistent mealtimes and carbohydrate intake. Coverage of post-lunch glucose often suboptimal. R must be injected at least 30 min before meal for better effect.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Pre-dinner R: based on bedtime BGM. Pre-dinner RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.
Twice-daily "split-mixed": N + R or N + RAA	Pre-breakfast: N ∼40% TDD + R or RAA ∼15% TDD. Pre-dinner: N ∼30% TDD + R or RAA ∼15% TDD.	Least number of injections for people with strong preference for this. Insulins can be mixed in one syringe. Least (N + R) or less (N + RAA) expensive insulins vs. analogs. Eliminates need for doses during the day.	Risk of hypoglycemia in afternoon or middle of night from N. Fixed mealtimes and meal content. Coverage of post-lunch glucose often suboptimal. Difficult to reach targets for blood glucose without hypoglycemia.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Evening R: based on bedtime BGM. Evening RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.

AID, automated insulin delivery; BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; LAA, long-acting analog; MDI, multiple daily injections; N, NPH insulin; R, short-acting (regular) insulin; RAA, rapid-acting analog; TBR, time below range; TDD, total daily insulin dose; TIR, time in range; URAA, ultra-rapid-acting analog (inhaled insulin may be considered if appropriate). Adapted from Holt et al. (4).

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daily injections of insulin (16,17). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (4). Integration of continuous glucose monitoring (CGM) into the treatment plan soon after diagnosis improves glycemic outcomes, decreases hypoglycemic events, and improves quality of life for individuals with type 1 diabetes (18–23). Its use is now considered standard of care for most people with type 1 diabetes (4) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level, with further improvements when using devices with predictive low-glucose insulin delivery suspension (24,25).

Automated insulin delivery (AID) systems are safe and effective for people with type 1 diabetes. Randomized controlled trials and real-world studies have demonstrated the ability of commercially available systems to improve achievement of glycemic goals while reducing the risk of hypoglycemia (26–31). Data are emerging on the safety and effectiveness of do-it-yourself systems (32,33). Evidence suggests that an AID hybrid closed-loop system is superior to AID sensor-augmented pump therapy for increased percentage of time in range and reduction of hypoglycemia (34,35).

Intensive insulin management using a version of CSII and CGM should be considered in individuals with type 1 diabetes whenever feasible. AID systems are preferred and should be considered for individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) to improve time in range and reduce A1C and hypoglycemia (26,28–31,36–42). When choosing among insulin delivery systems, individual preferences, cost, insulin type, dosing plan, and self-management capabilities should be considered. See Section 7, "Diabetes Technology," for a full discussion of insulin delivery devices.

In general, individuals with type 1 diabetes require approximately 30–50% of their daily insulin as basal and the remainder as prandial (43). This proportion depends on several factors, including but not limited to carbohydrate consumption, age, pregnancy status, and puberty stage (4,44–48). Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1 unit/kg/day. Higher amounts may be required during puberty, menses, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in adults with type 1 diabetes who are metabolically stable, with approximately one-half administered as prandial insulin given to manage blood glucose after meals and the remaining portion as basal insulin to manage glycemia in the periods between meal absorption (49). Starting doses and those soon after diagnosis may be higher, if an individual presents with ketoacidosis, or lower (0.2–0.6 units/kg), particularly in young children and those with continued endogenous insulin production (during the partial remission phase or "honeymoon period," or in people who present with type 1 diabetes in adulthood) (49–51). This guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (52).

Typical multidose treatment plans for individuals with type 1 diabetes combine premeal use of prandial insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best managed by a well-timed injection or inhalation of prandial insulin. Prandial insulin should ideally be administered prior to meal consumption; however, the optimal time to administer varies based on the pharmacokinetics of the formulation (regular, RAA, or inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demand for glucose. To address this variability in people treated with insulin, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education on how to adjust prandial insulin to account for nutritional intake and the correction dose based on premeal glucose levels, anticipated activity, and sick-day management can be effective and should be offered to most individuals (53–58). Education regarding adjustment of prandial insulin dose for glycemic trends should be provided to individuals who are using CGM alone or an AID system (59–62). Further adjustment of prandial insulin doses for nutritional intake of protein and fat, in addition to carbohydrates, is recommended but may be more feasible for individuals using CSII than for those using multiple daily injections (55). With some AID systems, use of a simplified meal announcement method may be an alternative for prandial insulin dosing (31,63). Assessment and education tailored to improve health literacy and numeracy may be necessary for individuals to effectively use various insulin dosing strategies and tools (64,65) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," and Section 7, "Diabetes Technology").

The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin plans and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (4).

Insulin Administration Technique

Ensuring that individuals and/or caregivers understand correct insulin administration technique is important to optimize glycemic management and insulin use safety. Recommendations have been published elsewhere outlining best practices for insulin administration (66). Proper insulin administration technique includes the following: injection, insertion of patch or infusion (for CSII or AID systems) into appropriate body areas, or oral inhalation (inhaled human insulin); injection or infusion site rotation; appropriate care of injection or infusion sites to avoid infection or other complications; avoidance of intramuscular (IM) insulin delivery; and filling of the reservoir (for bolus patch, CSII, or AID systems) or inhaler (for inhaled human insulin) depending on the method of administration. Selection of method of administration (vial and syringe, insulin pen, insulin patch, inhaled insulin, connected insulin pens/devices, or insulin pumps) will depend on a variety of individual-specific factors and needs, cost and coverage, and individual preferences. Reassessment of the appropriate administration technique should be completed during routine follow-up.

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Exogenously delivered insulin should be injected or infused into subcutaneous tissue, not intramuscularly. Recommended sites for insulin administration include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated compared with longer needles, including a study performed in adults with obesity (67).

Injection or infusion site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection or infusion site rotation and how to recognize and avoid injecting in areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin administration sites for the presence of lipohypertrophy, as well as assessment of administration device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection, infusion, or inhalation technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral noninsulin glucose-lowering medications have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (∼1 kg) with pramlintide (68). Similar results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes was associated with small reductions in body weight, insulin dose, and lipid levels but did not sustainably improve A1C (69,70). The largest clinical trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, and results showed modest A1C reductions (∼0.4%), decreases in weight (∼5 kg), and reductions in insulin doses (71,72). Liraglutide was also assessed for impact on C-peptide in individuals with type 1 diabetes and residual β-cell function. During treatment there was no impact, and with liraglutide discontinuation there was worsening of C-peptide loss compared with placebo (73). Retrospective case series have revealed potential benefits on body weight and glycemic metrics with addition of semaglutide or tirzepatide for individuals with type 1 diabetes and obesity (74,75). Prospective studies using semaglutide are ongoing (76,77).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C, reduced body weight, and improved blood pressure (78); however, SGLT2 inhibitor use in type 1 diabetes was associated with an increased rate of DKA (79). The SGLT1/2 inhibitor sotagliflozin has been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C and body weight (80); however, sotagliflozin use was associated with an eightfold increase in DKA compared with placebo (81). The studies that led to the approved indication for heart failure (HF) excluded individuals with type 1 diabetes or a history of DKA (82,83). See SGLT INHIBITION AND RISK OF KETOSIS, later in this section, and PREVENTION AND TREATMENT OF HEART FAILURE in Section 10, "Cardiovascular Disease and Risk Management," for information on risk mitigation with the use of SGLT inhibitors in those with type 1 diabetes. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on selection of candidates for treatment and precautions (84).

There are currently no approved therapies for preservation of C-peptide or delaying the progression of symptomatic type 1 diabetes. Higher C-peptide levels have been associated with better A1C, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia (85). Various therapies, including verapamil, menin inhibitors, Janus kinase inhibitors, antithymocyte globulin, several monoclonal antibodies including teplizumab, and cell therapies, are currently under active investigation.

SURGICAL TREATMENT OF TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous kidney transplantation, following kidney transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite optimized glycemic management (86). In much of the world, allogenic islet transplantation is regulated as an organ transplant. However, in the U.S., allogenic islet transplantation is regulated as a cell therapy, and the first such allogeneic islet cell therapy, donislecel-jujn, was approved in 2023. Donislecel is indicated for the treatment of adults with type 1 diabetes who are unable to reach their A1C goals because of repeated episodes of severe hypoglycemia despite intensive diabetes management and education (87). Alternative islet sources are currently under active investigation.

The 2021 ADA/EASD consensus report on the management of type 1 diabetes in adults offers a simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes (**Fig. 9.2**) (4).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.7 Healthy behaviors, diabetes self-management education and support, avoidance of therapeutic inertia, and social determinants of health should

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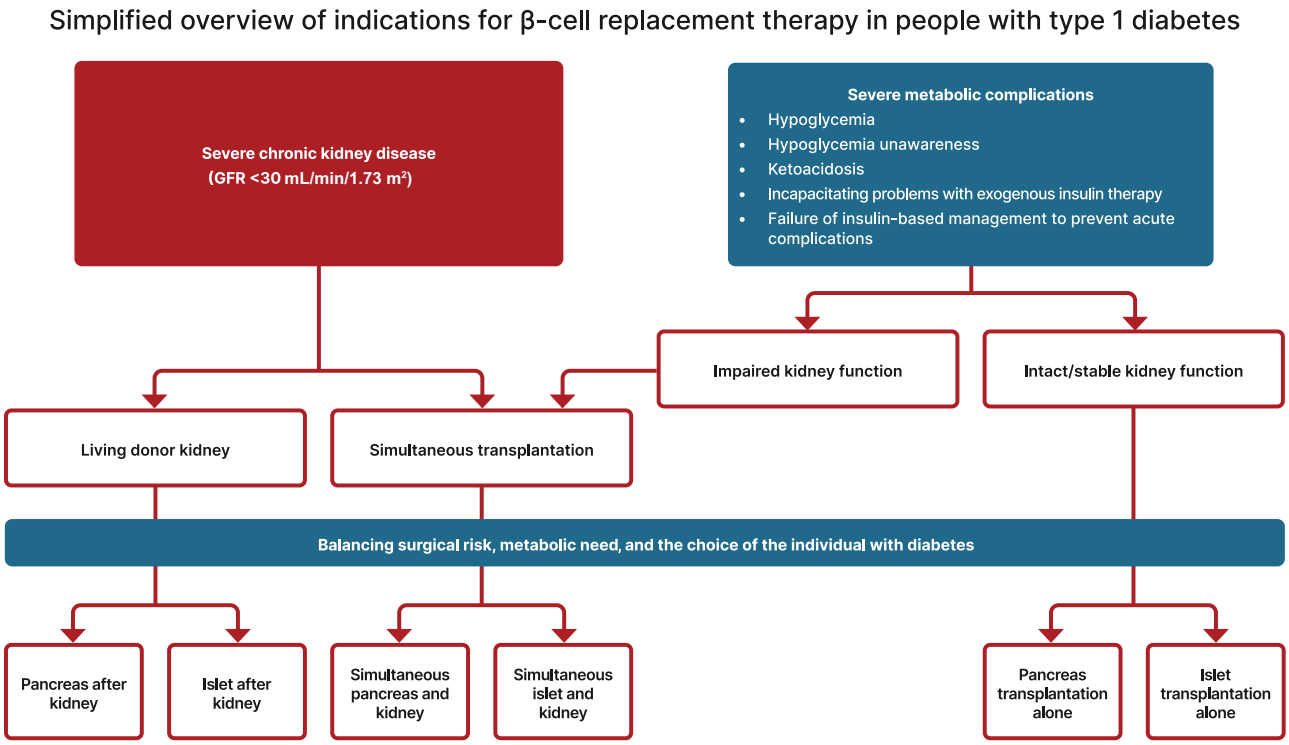
Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes
Severe chronic kidney disease (GFR <30 mL/min/1.73 m²)
Severe metabolic complications
Hypoglycemia
Hypoglycemia unawareness
Ketoacidosis
Incapacitating problems with exogenous insulin therapy
Failure of insulin-based management to prevent acute complications
Impaired kidney function
Intact/stable kidney function
Living donor kidney
Simultaneous transplantation
Balancing surgical risk, metabolic need, and the choice of the individual with diabetes
Pancreas after kidney
Islet after kidney
Simultaneous pancreas and kidney
Simultaneous islet and kidney
Pancreas transplantation alone
Islet transplantation alone

Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation and islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the individual has end-stage kidney disease, which may be performed simultaneously or after kidney transplantation. All decisions about transplantation must consider the surgical risk, metabolic need, and the choices of the individual with diabetes. GFR, glomerular filtration rate. Adapted from Holt et al. (4).

be included in the glucose-lowering management of type 2 diabetes. **A**

9.8 A person-centered shared decision-making approach should guide the choice of glucose-lowering medications for adults with type 2 diabetes. Use medications that provide sufficient effectiveness to achieve and maintain intended treatment goals with consideration of the effects on cardiovascular, kidney, weight, and other relevant comorbidities; hypoglycemia risk; cost and access; risk for adverse reactions and tolerability; and individual preferences (**Fig. 9.3** and **Table 9.2**). **E**

9.9 Combination therapy can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals. **A**

9.10 In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, the treatment plan should include medications with demonstrated benefits to reduce cardiovascular events (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] and/or sodium–glucose cotransporter 2 [SGLT2] inhibitor) for glycemic management and comprehensive cardiovascular risk reduction (irrespective of A1C) (**Fig. 9.3** and **Table 9.2**). **A**

9.11 In adults with type 2 diabetes who have heart failure (HF) (with either reduced or preserved ejection fraction), an SGLT2 inhibitor is recommended for both glycemic management and prevention of HF hospitalizations (irrespective of A1C) (**Fig. 9.3**). **A**

9.12 In adults with type 2 diabetes and symptomatic heart failure with preserved ejection fraction (HFpEF) and obesity, a GLP-1 RA with demonstrated benefits for both glycemic management and reduction of HF-related symptoms (irrespective of A1C) is recommended. **A**

9.13 In adults with type 2 diabetes who have CKD (with confirmed estimated glomerular filtration rate [eGFR] 20–60 mL/min/1.73 m^2 and/or albuminuria), an SGLT2 inhibitor or GLP-1 RA with demonstrated benefit in this population should be used for both glycemic management (irrespective of A1C) and for slowing progression of CKD and reduction in cardiovascular events (**Fig. 9.3**). The glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min/1.73 m^2. **A**

9.14 In adults with type 2 diabetes and advanced CKD (eGFR <30 mL/min/1.73 m^2), a GLP-1 RA is preferred for glycemic management due to lower risk of hypoglycemia and for cardiovascular event reduction. **B**

9.15 In adults with type 2 diabetes, metabolic dysfunction–associated steatotic liver disease (MASLD), and overweight or obesity, consider using a GLP-1 RA or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA with potential benefits in metabolic dysfunction–associated steatohepatitis (MASH) for glycemic management and as an adjunctive to healthy interventions for weight loss. **B**

9.16a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management due to potential beneficial effects on MASH. **B**

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9.16b Combination therapy with pioglitazone plus a GLP-1 RA can be considered for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) due to potential beneficial effects on MASH. **B**

9.17 Medication plan and medication-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.2**). **E**

9.18 Treatment modification (intensification or deintensification) for adults not meeting individualized treatment goals should not be delayed. **A**

9.19 Choice of glucose-lowering therapy modification should take into consideration individualized glycemic and weight goals, presence of comorbidities (cardiovascular, kidney, liver, and other metabolic comorbidities), and the risk of hypoglycemia. **A**

9.20 When initiating a new glucose-lowering medication, reassess the need for and/or dose of medications with higher hypoglycemia risk (i.e., sulfonylureas, meglitinides, and insulin) to minimize the risk of hypoglycemia and treatment burden. **A**

9.21 Concurrent use of dipeptidyl peptidase 4 (DPP-4) inhibitors with a GLP-1 RA or a dual GIP and GLP-1 RA is not recommended due to lack of additional glucose lowering beyond that of a GLP-1 RA alone. **B**

9.22 In adults with type 2 diabetes who have not achieved their individualized weight goals, additional weight management interventions (e.g., intensification of lifestyle modifications, structured weight management programs, pharmacologic agents, or metabolic surgery, as appropriate) are recommended. **A**

9.23 In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if symptoms of hyperglycemia are present or when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]). **E**

9.24 In adults with type 2 diabetes and no evidence of insulin deficiency, a GLP-1 RA, including a dual GIP and GLP-1 RA, is preferred to insulin (**Fig. 9.4**). **A**

9.25 If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. **A**

9.26 In adults with type 2 diabetes who are initiating insulin therapy, continue glucose-lowering agents (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (i.e., weight, cardiometabolic, or kidney benefits). **A**

A holistic, multifaceted, person-centered approach that accounts for the complexity of managing type 2 diabetes and its complications across the life span is recommended. Person-specific factors that affect choice of treatment include individualized glycemic goals (see Section 6, "Glycemic Goals and Hypoglycemia"), individualized weight goals (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), the individual's risk for hypoglycemia, and the individual's history of or risk factors for cardiovascular, kidney, liver, and other comorbidities and complications of diabetes (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). In addition, treatment decisions must consider the tolerability and side effect profiles of medications, complexity of the medication plan and the individual's capacity to implement it given their specific situation and context, and the access, cost, and availability of medications. Lifestyle modifications and health behaviors that improve health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") should be emphasized along with any pharmacologic therapy. Section 13, "Older Adults," and Section 14, "Children and Adolescents," have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management," have recommendations for the use of glucose-lowering drugs in the management of cardiovascular disease and kidney disease, respectively.

Choice of Glucose-Lowering Therapy

Healthy lifestyle behaviors, diabetes self-management education and support (DSMES), avoidance of therapeutic inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities, considerations of adverse effects (including hypoglycemia) and treatment burden, and treatment goals and preferences. Shared decision-making can be facilitated during clinical encounters through use of decision aides and has been shown to improve A1C in adults with type 2 diabetes, though in clinical trials the benefits of shared decision-making were limited to face-to-face discussions (not online encounters) and to individuals with elevated A1C (>8%) (88). Pharmacotherapy should be started at the time type 2 diabetes is diagnosed, without delay, unless there are contraindications. Medication plans should have adequate efficacy to achieve and maintain individualized treatment goals with respect to glucose lowering, reduction of cardiovascular and kidney disease risks, weight management, and impacts on other health conditions and treatment burden. In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD), the treatment plan should include agents that reduce cardiovascular and kidney disease risk (**Fig. 9.3** and **Table 9.2**) (see also Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management").

In individuals without ASCVD, HF, or CKD, choice of therapy should be informed by considerations of weight management (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), mitigation of

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metabolic dysfunction–associated liver disease (MASLD) or metabolic dysfunction–associated steatohepatitis (MASH) risk (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"), and achievement and maintenance of individualized glycemic goals. In general, higher-efficacy approaches, including combination therapy, have greater likelihood of achieving treatment goals. Weight management is a distinct treatment goal, along with glycemic management, as it has multifaceted benefits, including reduction of A1C, reduction in hepatic steatosis, and improvement in cardiovascular risk factors (89–91). For individuals with type 2 diabetes who require initiation or intensification of glucose-lowering therapy to achieve and/or maintain individualized glycemic goals and who do not have additional considerations informing choice of therapy beyond need for glucose lowering, metformin is a commonly used medication that historically has been the first-line treatment for type 2 diabetes (92,93). Metformin is effective and safe, is inexpensive and widely available, and reduces risks of microvascular complications, cardiovascular events, and death (92,94,95). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, is weight neutral, does not cause hypoglycemia, and reduces cardiovascular mortality (96). Metformin is also more effective than dipeptidyl peptidase 4 (DPP-4) inhibitors in lowering A1C and weight when used as monotherapy (97).

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration and/or using extended-release formulation. The drug is cleared by kidney filtration, and metformin may be safely used in people with estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 (98). Very high circulating levels (e.g., as a result of overdose or acute kidney injury) have been associated with lactic acidosis (99). However, the occurrence of this complication is very rare (100) and primarily occurs when the estimated glomerular filtration rate (eGFR) is $<$30 mL/min/1.73 m^2 (101). For people with an eGFR of 30–45 mL/min/1.73 m^2, there is an increased risk for periodic decreases of eGFR to $\leq$30 mL/min/1.73 m^2 which heightens the risk of lactic acidosis. Metformin use is also associated with increased risk of vitamin B12 deficiency and worsening of symptoms of neuropathy (102,103), suggesting periodic testing of vitamin B12 levels (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities").

The comparative glucose-lowering efficacy of different pharmacologic agents has been examined primarily in network meta-analyses, as few prospective clinical trials have compared multiple drug classes head-to-head. In general, the largest reductions in A1C levels are achieved by treatment plans that include insulin, select GLP-1 RAs (particularly semaglutide), and tirzepatide, while DPP-4 inhibitors resulted in the smallest reductions in A1C (104–106). In A Diabetes Outcome Progression Trial (ADOPT), rosiglitazone monotherapy was more effective than metformin and glyburide monotherapies in achieving and maintaining fasting plasma glucose below 180 mg/dL (10 mmol/L) among recently diagnosed individuals with type 2 diabetes whose baseline fasting plasma glucose was 126–180 mg/dL (7–10 mmol/L), while glyburide was least effective (107). More recently, the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) trial compared use of insulin glargine U-100, liraglutide, sitagliptin, and glimepiride as add-on treatments to metformin monotherapy among individuals with type 2 diabetes and baseline A1C 6.8–8.5% (108). It found that at 5 years, all therapies decreased A1C levels but glargine and liraglutide were modestly more effective in achieving and maintaining A1C below 7%, while sitagliptin was least effective. Severe hypoglycemia was significantly more common in those prescribed glargine or glimepiride. An observational study that emulated many of GRADE's design features and included canagliflozin as a comparator arm, but did not include insulin glargine, found that liraglutide was more effective at achieving and maintaining A1C below 7% than sitagliptin, canagliflozin, or glimepiride, which all had comparable effectiveness (108).

Thus, when choosing a glucose-lowering medication to achieve individualized glycemic goals, we recommend engaging in shared decision-making and considering factors such as glucose-lowering efficacy, the side effect profile, and medication accessibility and affordability (108). In all cases, treatment plans need to be continuously reviewed for efficacy, side effects, hypoglycemia, and treatment burden (**Table 9.2**).

When A1C is $\geq$1.5% above the individualized glycemic goal (see Section 6, "Glycemic Goals and Hypoglycemia," for appropriate goals), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their goal A1C level (89) (**Fig. 9.3** and **Table 9.2**). Insulin should be considered as part of any combination medication plan when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, and ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels $\geq$300 mg/dL ($\geq$16.7 mmol/L) or A1C $>$10% ($>$86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (unexpected weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the medication plan and/or changing to noninsulin agents is possible. Additionally, there is evidence that people with type 2 diabetes and severe hyperglycemia can also be effectively treated with a sulfonylurea, a GLP-1 RA, or dual GIP and GLP-1 RA, though evidence is scarce for individuals with baseline A1C above 10–12% (104,109–111). GLP-1 RAs and tirzepatide have additional benefits over insulin and sulfonylureas, specifically lower risks for hypoglycemia (both) and favorable weight (both), cardiovascular (GLP-1 RAs), kidney (GLP-1 RAs), and liver (both) end points.

Combination Therapy

Because type 2 diabetes is a progressive disease, maintenance of glycemic goals often requires combination therapy. Traditional recommendations have called for the use of stepwise addition of medications to metformin to maintain A1C goals. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and reduce potential side effects and expense (112). However, some data support initial combination therapy for more rapid attainment of glycemic goals (113,114) and later combination therapy for longer durability of glycemic effect (115). Initial combination therapy should be considered in people presenting

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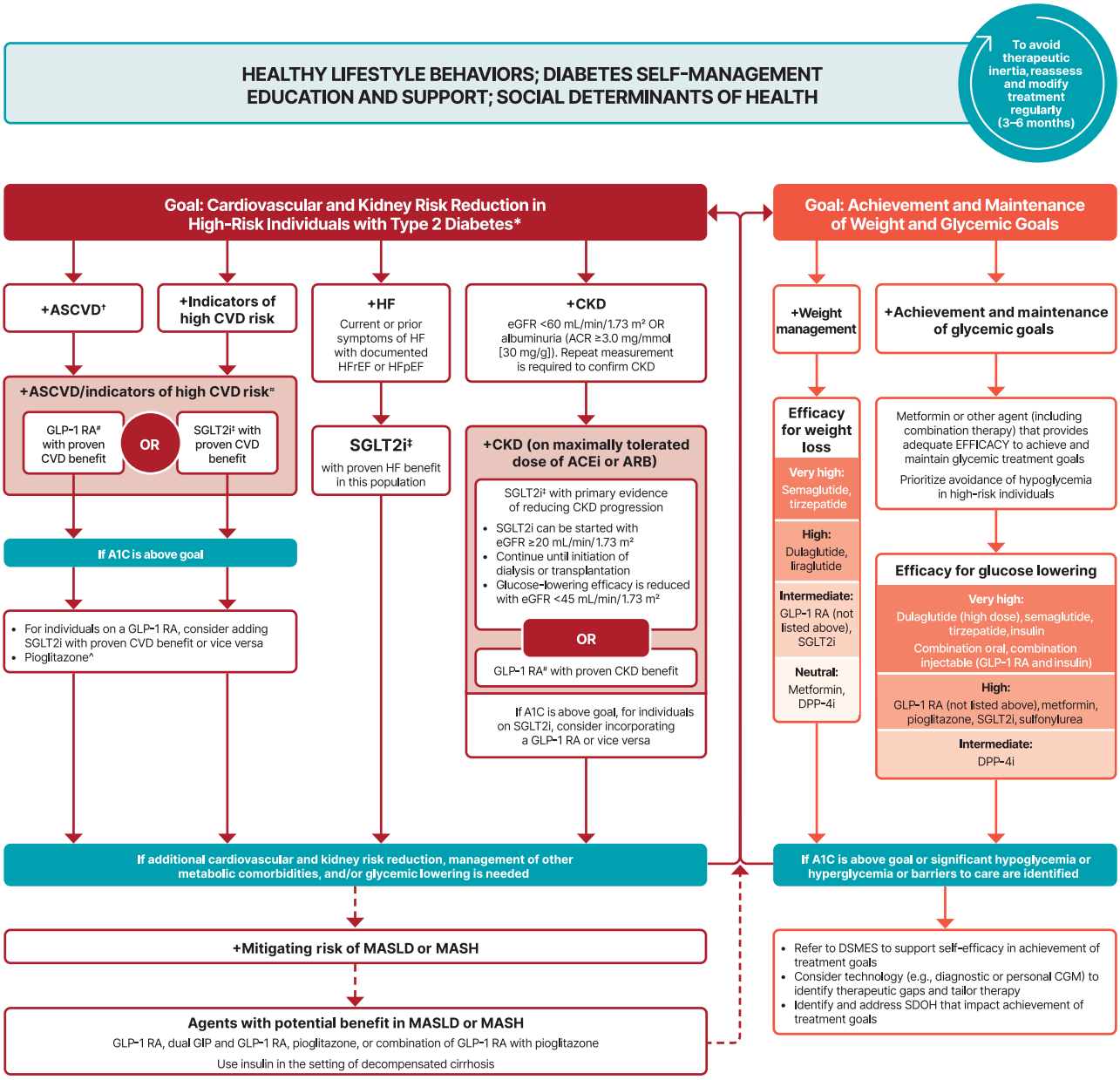
Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes


HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH
To avoid therapeutic inertia, reassess and modify treatment regularly (3–6 months)
Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*
Goal: Achievement and Maintenance of Weight and Glycemic Goals
+ASCVD†
+Indicators of high CVD risk
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD
+Weight management
+Achievement and maintenance of glycemic goals
+ASCVD/indicators of high CVD risk≈
GLP-1 RA# with proven CVD benefit
OR
SGLT2i‡ with proven CVD benefit
SGLT2i‡ with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi or ARB)
SGLT2i‡ with primary evidence of reducing CKD progression
SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
Continue until initiation of dialysis or transplantation
Glucose-lowering efficacy is reduced with eGFR <45 mL/min/1.73 m²
OR
GLP-1 RA# with proven CKD benefit
If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa
Efficacy for weight loss
Very high: Semaglutide, tirzepatide
High: Dulaglutide, liraglutide
Intermediate: GLP-1 RA (not listed above), SGLT2i
Neutral: Metformin, DPP-4i
Metformin or other agent (including combination therapy) that provides adequate EFFICACY to achieve and maintain glycemic treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals
Efficacy for glucose lowering
Very high: Dulaglutide (high dose), semaglutide, tirzepatide, insulin
Combination oral, combination injectable (GLP-1 RA and insulin)
High: GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea
Intermediate: DPP-4i
If A1C is above goal
For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
Pioglitazone^
If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities, and/or glycemic lowering is needed
If A1C is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified
+Mitigating risk of MASLD or MASH
Refer to DSMES to support self-efficacy in achievement of treatment goals
Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of treatment goals
Agents with potential benefit in MASLD or MASH
GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1 RA with pioglitazone
Use insulin in the setting of decompensated cirrhosis

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. The left side of the algorithm prioritizes mitigation of diabetes-related complications and end-organ effects, while the right side addresses weight and glucose management goals. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; DSMES, diabetes self-management education and support; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes. Adapted from Davies et al. (89).

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Table 9.2—Features of medications for lowering glucose in type 2 diabetes

Medication (route of administration)	Glucose-lowering efficacy[1]	Hypoglycemia risk	Weight effects[2]	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
Metformin (oral)	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m^2	Neutral	• GI side effects: mitigate with slow dose titration, extended-release formulations, and administration with food. • Potential for vitamin B12 deficiency: monitor and replete as appropriate.
SGLT2 inhibitors (oral)	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels of individual agents for dosage considerations for kidney function • Glucose-lowering effect is minimal at eGFR <45 mL/min/1.73 m^2 and lower; continue for cardiovascular and kidney benefit until dialysis or transplantation	Unknown	• DKA risk in individuals with insulin deficiency (rare in T2D): discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentations (including euglycemic DKA); mitigate risk with sick-day planning; discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting. • Genital mycotic infections: mitigate risk with genital hygiene and avoid use in high-risk individuals. • Necrotizing fasciitis of the perineum (Fournier gangrene): rare; prompt treatment if suspected. • Intravascular volume depletion: attention to volume status and blood pressure, particularly when ill or fasting; adjust other volume-contracting agents as applicable; monitor kidney function upon initiation.
GLP-1 RAs (SQ; semaglutide also available in oral formulation)	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ) Demonstrated benefit for progression of CKD for semaglutide (SQ)	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment for dulaglutide, liraglutide, or semaglutide • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	• Thyroid C-cell tumors identified in rodents; human relevance not determined. • Ileus: risk level is not well established; provide guidance on discontinuation prior to surgical procedures. • Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected. • Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals. • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]). • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including of oral contraceptives). • GI side effects: counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g. stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	
DPP-4 inhibitors (oral)	Intermediate	No	Neutral	Neutral	Neutral (potential risk: saxagliptin)	Neutral	• Dose adjustment required based on kidney function (sitagliptin, saxagliptin, alogliptin) • No dose adjustment required for linagliptin	Unknown	• Pancreatitis has been reported, but causality has not been established. Discontinue if pancreatitis is suspected. • Postmarketing concerns about joint pain (consider discontinuing if debilitating and other treatment options are feasible) and bullous pemphigoid (discontinue if suspected).
Pioglitazone (oral)	High	No	Gain	Potential benefit	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in kidney impairment due to potential for fluid retention	Potential benefit	• Increased risk of HF and fluid retention. Do not use in the setting of HF. • Risk of bone fractures. • Bladder cancer: do not use in individuals with active bladder cancer, and use caution in those with prior history of bladder cancer.
Sulfonylureas (2nd generation) (oral)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in CKD • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Unknown	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text). • Use with caution in individuals at risk for hypoglycemia, particularly if in combination with insulin.
Insulin (human) (SQ; regular insulin also available as inhaled formulation) **Insulin (analogs)** (SQ)	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	Unknown	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs • Risk of hypoglycemia and duration of activity increases with the severity of impaired kidney function. • Refer to device-specific instructions for insulins compatible with different delivery systems (i.e., pumps, connected insulin pens, insulin patches).

CKD, chronic kidney disease; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (106). [2]Tsapas et al. (241). Adapted from Davies et al. (89).

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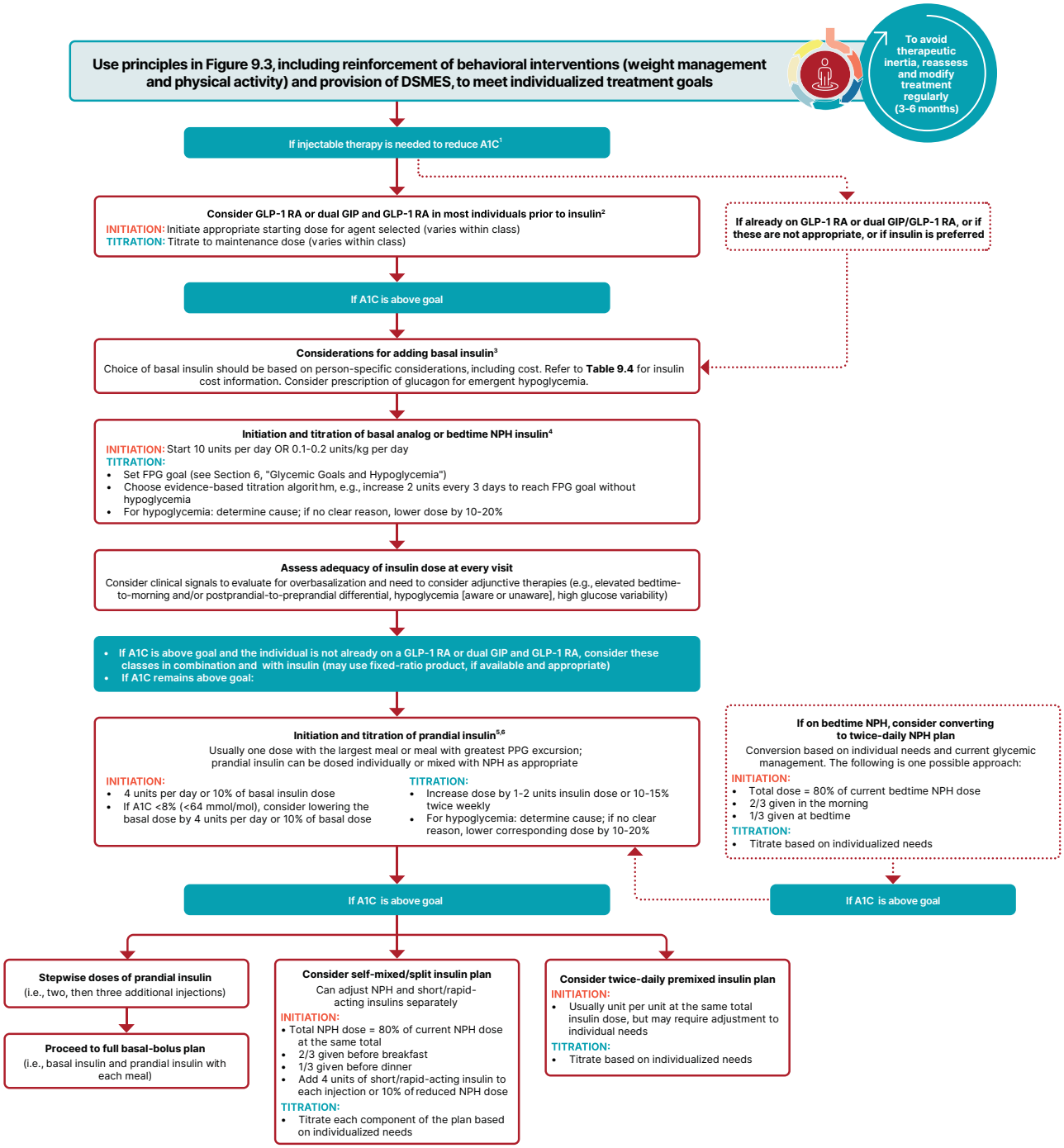
Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals
To avoid therapeutic inertia, reassess and modify treatment regularly (3-6 months)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA or dual GIP and GLP-1 RA in most individuals prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or dual GIP/GLP-1 RA, or if these are not appropriate, or if insulin is preferred
If A1C is above goal
Considerations for adding basal insulin[3]
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to Table 9.4 for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.
Initiation and titration of basal analog or bedtime NPH insulin[4]
INITIATION: Start 10 units per day OR 0.1-0.2 units/kg per day
TITRATION:
• Set FPG goal (see Section 6, "Glycemic Goals and Hypoglycemia")
• Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG goal without hypoglycemia
• For hypoglycemia: determine cause; if no clear reason, lower dose by 10-20%
Assess adequacy of insulin dose at every visit
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., elevated bedtime-to-morning and/or postprandial-to-preprandial differential, hypoglycemia [aware or unaware], high glucose variability)
• If A1C is above goal and the individual is not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes in combination and with insulin (may use fixed-ratio product, if available and appropriate)
• If A1C remains above goal:
Initiation and titration of prandial insulin[5,6]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
• 4 units per day or 10% of basal insulin dose
• If A1C <8% (<64 mmol/mol), consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION:
• Increase dose by 1-2 units insulin dose or 10-15% twice weekly
• For hypoglycemia: determine cause; if no clear reason, lower corresponding dose by 10-20%
If on bedtime NPH, consider converting to twice-daily NPH plan
Conversion based on individual needs and current glycemic management. The following is one possible approach:
INITIATION:
• Total dose = 80% of current bedtime NPH dose
• 2/3 given in the morning
• 1/3 given at bedtime
TITRATION:
• Titrate based on individualized needs
If A1C is above goal
If A1C is above goal
Stepwise doses of prandial insulin
(i.e., two, then three additional injections)
Proceed to full basal-bolus plan
(i.e., basal insulin and prandial insulin with each meal)
Consider self-mixed/split insulin plan
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
• Total NPH dose = 80% of current NPH dose at the same total
• 2/3 given before breakfast
• 1/3 given before dinner
• Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
• Titrate each component of the plan based on individualized needs
Consider twice-daily premixed insulin plan
INITIATION:
• Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
• Titrate based on individualized needs

1. Consider insulin as the first injectable if symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, and frequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit; oral or injectable GLP-1 RAs are appropriate.
3. For people on GLP-1 RA and basal Insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with a morning dose of a long-acting basal Insulin. Consider dosing NPH in the morning for steroid-induced hyperglycemia.
5. Prandial insulin options include injectable rapid- and ultra-rapid-acting analog insulins, injectable short-acting human insulin, or inhaled human insulin.
6. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; PPG, postprandial glucose. Adapted from Davies et al. (242).

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with A1C levels 1.5–2.0% above their individualized goal. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular and kidney disease risk reduction (e.g., GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors) may reduce the need for agents that increase the risks of hypoglycemia and weight gain or are less well tolerated. Thus, treatment intensification requires purposeful selection of medications in alignment with multiple individualized person-centered treatment goals simultaneously (**Fig. 9.3**).

Treatment intensification, deintensification, or modification, as appropriate, for people not meeting individualized treatment goals should not be delayed (therapeutic inertia) (116). Results from comparative effectiveness meta-analyses suggest that each new class of oral noninsulin agents when added to metformin generally lowers A1C by approximately 0.7–1.0% (8–11 mmol/mol). Addition of GLP-1 RAs or the dual GIP and GLP-1 RA to metformin usually results in 1 to ≥2% lowering of A1C (104,117,118) (**Fig. 9.3** and **Table 9.2**). We do not recommend using GLP-1 RAs (or the dual GIP and GLP-1 RA) together with a DPP-4 inhibitor as there is no added glucose-lowering benefit beyond that of the GLP-1 RA alone (119–121).

When even greater potency of glucose reduction is needed, basal insulin, either human NPH or a long-acting insulin analog, should be initiated. However, if the individual is not already receiving GLP-1 RA or dual GIP and GLP-1 RA therapy, an agent from these classes should be started first, as it may be sufficient for achieving individualized A1C goals but with lower risk of hypoglycemia and with favorable weight, cardiovascular, kidney, and liver profiles. While most GLP-1 RAs are injectable medications, an oral formulation of semaglutide is commercially available (122). In trials analyzing the addition of an injectable GLP-1 RA, dual GIP and GLP-1 RA, or insulin in people needing further glucose lowering, glycemic efficacies of GLP-1 RAs and the dual GIP and GLP-1 RA were similar to or greater than that of basal insulin (123–130). GLP-1 RAs and dual GIP and GLP-1 RA in these trials also had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support high-potency GLP-1 RAs and dual GIP and GLP-1 RA as the preferred options for individuals requiring more intensive glucose management (**Fig. 9.4**).

In individuals who are intensified to insulin therapy, combination therapy with a GLP-1 RA or a dual GIP and GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effects, as well as weight and hypoglycemia benefits, than treatment intensification with insulin alone (89,131). However, cost, accessibility, and tolerability are important considerations for GLP-1 RA and dual GIP and GLP-1 RA use.

In all cases, treatment plans need to be continuously reviewed for efficacy, side effects (including hypoglycemia), and treatment burden (**Table 9.2**). In some instances, the individual will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, hypoglycemia, intolerable side effects, new contraindications, expense, or a change in glycemic goals (e.g., in response to development of comorbidities). See below for cost considerations of glucose-lowering therapies (MEDICATION COSTS AND AFFORDABILITY). Section 13, "Older Adults," has a full discussion of treatment considerations in older adults. Treatment deintensification may also be needed in the setting of weight loss and/or optimization of lifestyle behaviors, when fewer pharmacologic agents are needed to maintain A1C goals. In this case, we recommend preferential deescalation of therapies that are most likely to cause side effects, hypoglycemia, and/or treatment burden and do not have cardiovascular, kidney, or metabolic benefits for continued use.

Glucose-Lowering Therapy for People With Cardiovascular Disease or Risk Factors for Cardiovascular Disease

For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated cardiovascular benefit (**Table 9.2**) is recommended independent of A1C, with or without metformin use, and in consideration of person-specific factors (**Fig. 9.3**). Individuals with these comorbidities already achieving their individualized glycemic goals with other medications may benefit from switching to these preferred medications to reduce risk of ASCVD, HF, and/or CKD in addition to achieving glycemic goals (see Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). This is particularly important because SGLT2 inhibitors and GLP-1 RAs are associated with lower risk of hypoglycemia and individuals with ASCVD, HF, and CKD have higher hypoglycemia risk than individuals without these conditions (132).

Individuals at lower risk for ASCVD may still benefit from GLP-1 RA therapy to reduce their risk of future cardiovascular events. The GRADE trial, which was designed to examine the comparative effectiveness of insulin glargine U-100, glimepiride, liraglutide, and sitagliptin in individuals with relatively short duration of diabetes (and, due to study eligibility criteria, low ASCVD risk) with respect to achieving and maintaining A1C below 7%, found that individuals treated with liraglutide had a slightly lower risk of cardiovascular disease than individuals receiving the other three treatments (hazard ratio 0.7 [95% CI 0.6–0.9]), although no significant differences were found for major adverse cardiovascular events, hospitalization for HF, or cardiovascular death (133). Individuals with type 2 diabetes and moderate levels of CVD risk appear to derive cardiovascular and mortality benefits with preferential use of GLP-1 RA and SGLT2 inhibitors compared with sulfonylurea or DPP-4 inhibitors (134). Similarly, while greater reductions in HF hospitalization risk are observed with SGLT2 inhibitor therapy in individuals with higher baseline HF risk, some benefit is observed across the full range of HF risk (135).

Glucose-Lowering Therapy for People With Chronic Kidney Disease

For individuals with type 2 diabetes and CKD, considerations for selection of glucose-lowering medications include their effectiveness and safety when eGFR is reduced as well as the potential to impact CKD progression, CVD risk, and hypoglycemia (136). Preferred medications for glucose management in individuals with CKD are GLP-1 RAs and SGLT2 inhibitors (can be initiated if eGFR is above 20 mL/min/1.73 m^2). GLP-1 RAs are effective in lowering glucose levels, regardless of kidney function, with a low risk for hypoglycemia, and a recent clinical trial suggests that the GLP-1 RA semaglutide has a beneficial effect on CVD, mortality, and kidney outcomes among people with CKD,

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leading to the recommendation that semaglutide can be used as another first-line agent for people with CKD (137,138). Other GLP-1 RAs (liraglutide and dulaglutide) may also have CKD benefits, but no other dedicated kidney trials have been published. Similarly, no dedicated kidney outcomes studies for the dual GIP and GLP-1 RA (tirzepatide) have been published. Dedicated kidney outcomes trials in people with CKD and type 2 diabetes have shown that the SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin have beneficial effects on slowing progression of CKD and CV outcomes in this population (139–141). However, their ability to lower glucose levels declines when the eGFR falls below 45 mL/min/1.73 m^2 (142–144). Metformin is also a preferred agent for those with CKD due to its well-documented efficacy and safety profile for all people with type 2 diabetes. However, there is no documented direct kidney benefit. Importantly, metformin should not be started in those whose eGFR is $<$45 mL/min/1.73 m^2. For those already treated with metformin, the dose of metformin should be reduced once eGFR is $<$45 mL/min/1.73 m^2 and should be stopped once eGFR is $<$30 mL/min/1.73 m^2 (98). A secondary analysis of the GRADE trial found that insulin glargine, liraglutide, sitagliptin, and glimepiride did not prevent the development of CKD when added to metformin monotherapy in individuals without underlying CKD (145). Importantly, an SGLT2 inhibitor was not included in the GRADE trial.

Individuals with CKD, particularly advanced CKD and kidney failure, are at high risk for hypoglycemia (132). If treated with insulin and/or sulfonylureas, treatment needs to be closely monitored and adjusted as eGFR declines and individuals need to be educated about and closely monitored for hypoglycemia occurrence (136). See Section 11, "Chronic Kidney Disease and Risk Management," for more details about prevention and treatment of CKD in individuals with diabetes.

Glucose-Lowering Therapy for People With Metabolic Comorbidities

Many adults with diabetes, either type 2 diabetes or type 1 diabetes, with obesity are at high risk of developing MASLD or MASH as well as MASH cirrhosis. Hence, the presence of MASLD or MASH should be a consideration when choosing glucose-lowering therapies. Accruing randomized clinical trial data suggest that pioglitazone, GLP-1 RA, and a dual GIP and GLP-1 RA have potential benefits in terms of decreasing hepatic steatosis and in the resolution of MASH without worsening of fibrosis in individuals with biopsy-proven MASH or those at higher risk of clinically significant liver fibrosis identified with noninvasive tests (146–153). Combination therapy with pioglitazone plus GLP-1 RA should also be considered for treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at higher risk of clinically significant liver fibrosis identified with noninvasive tests, as such therapy is safe and effective and has been shown to reduce hepatic steatosis (154–156). It is important to note that these studies are based on phase 2 clinical trials and await further phase 3 confirmation of evidence. However, these plans are preferred as they offer potential benefit compared with lack of histological benefit (or clinical trial data) from other glucose-lowering therapies in MASLD. Further details regarding liver health in diabetes can be found in Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities."

Obesity is present in over 90% of people with type 2 diabetes, and in these individuals weight management is a key treatment goal, along with glucose lowering. In the setting of obesity, the choice of glucose-lowering medications should take into consideration their effects on weight. Insulins, sulfonylureas, and thiazolidinediones can promote weight gain and should be used judiciously and at the lowest possible dose. Glucose-lowering medications that promote weight loss should be prioritized. Of the currently available agents, tirzepatide and semaglutide have the highest efficacy in terms of glucose lowering as well as weight loss, followed by dulaglutide, liraglutide, and extended-release exenatide (157–161). Other glucose-lowering medications (metformin, SGLT2 inhibitors, DPP-4 inhibitors, dopamine agonists, bile acid sequestrants, and α-glucosidase inhibitors) are weight neutral or have a modest beneficial effect on weight. These medications can be used as add-on therapies in people with type 2 diabetes and obesity who require additional glucose lowering or if the more effective medications are not tolerated, are contraindicated, or are unavailable. Metabolic surgery, especially Roux-en-Y gastric bypass and sleeve gastrectomy, are very effective interventions to achieve both weight and glycemic goals and have additional health benefits beyond improving metabolism (162). Further details regarding treatment of obesity can be found in Section 8 ("Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See INSULIN ADMINISTRATION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to individuals with diabetes, and clinicians should avoid using insulin as a threat or describing it as a sign of personal failure. The utility and importance of insulin to achieve and maintain glycemic goals once progression of the disease overcomes the effect of other agents as well as for temporary use for acute situations (such as hospitalization, acute illness, or high-dose glucocorticoid therapy) should be emphasized. Educating and involving people with diabetes in insulin management is beneficial. For example, instruction of individuals with type 2 diabetes initiating insulin on self-titration of insulin doses based on glucose monitoring improves glycemic management (163). Comprehensive education regarding glucose monitoring, nutrition, physical activity, contingency planning (for illness, fasting, or medication unavailability), and the prevention and appropriate treatment of hypoglycemia are critically important for all individuals using insulin. Assessment and education tailored to improve health literacy and numeracy may be necessary for individuals to effectively use various insulin dosing strategies and tools (64,65). See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for guidance on diabetes self-management education.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to noninsulin glucose-lowering medications. For individuals with type 2 diabetes, starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as

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needed to achieve and maintain glycemic goals. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (164,165). Attainment of fasting glucose goals can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine and detemir) have been demonstrated to reduce the risk of level 2 hypoglycemia and nocturnal hypoglycemia compared with NPH insulin (166). Longer-acting basal analogs (U-300 glargine or degludec) convey a lower nocturnal hypoglycemia risk than U-100 glargine (167,168). It is important to understand how to convert individuals from one basal insulin to another, as switching insulins may be required due to the availability of more clinically appropriate insulin alternatives, removal of a product from the market (i.e., insulin detemir), or changes to insurance coverage. Often doses can be converted unit for unit and subsequently adjusted based on glucose monitoring; however, an initial dose reduction of 10–20% can be used for individuals in very tight management or at high risk for hypoglycemia and is typically needed when switching from insulin detemir or U-300 glargine to another insulin (169). Clinicians should also be aware of the potential for overbasalization with insulin therapy (i.e., use of higher than clinically necessary and appropriate dose of basal insulin, typically masking insufficient mealtime insulin). Clinical signals that should prompt evaluation for overbasalization include high bedtime-to-morning or preprandial-to-postprandial glucose differential (e.g., bedtime-to-morning glucose differential ≥50 mg/dL [≥2.8 mmol/L]), hypoglycemia (aware or unaware), and high glucose variability. Evidence of overbasalization should prompt reevaluation of the glucose-lowering treatment plan to better address postprandial hyperglycemia (170).

Combination Injectable Therapy and Prandial Insulin

If basal insulin has been titrated to an acceptable fasting blood glucose level and A1C remains above goal, if there is evidence of significant postprandial hyperglycemia, or if signs of overbasalization are present, advancement to combination injectable therapy is necessary (**Fig. 9.4**). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of prandial insulin (131,171). If an individual is not already being treated with a GLP-1 RA or dual GIP and GLP-1 RA, a GLP-1 RA (either as an individual product or in a fixed-ratio combination with a basal insulin product) or dual GIP and GLP-1 RA should be considered prior to starting prandial insulin to address prandial management and to lower the risks of hypoglycemia and weight gain associated with insulin therapy (131,172).

Further intensification of insulin therapy entails adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a plan with multiple prandial doses if necessary (173). We suggest starting with a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion. The prandial insulin plan can then be intensified based on individual needs (**Fig. 9.4**). Alternatively, for an individual treated with basal insulin in whom additional prandial coverage is desired but administering insulin prior to one or more meals is not feasible, the medication plan can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal-prandial plans offer greater flexibility for individuals who eat on irregular schedules, have variable meal content, or otherwise benefit from greater individualization and flexibility in insulin administration. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (for example, 70/30) formulations, are often less costly alternatives to insulin analogs.

Individuals with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (174). Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported meaningful differences in A1C or hypoglycemia (175,176). Titration of prandial insulin can be based on home self-monitored blood glucose or CGM. When significant additions to the prandial insulin dose are made, particularly with the evening meal, consideration should be given to decreasing basal insulin to reduce risk of hypoglycemia. When initiating intensification of insulin therapy, metformin, SGLT2 inhibitors, and GLP-1 RAs (or a dual GIP and GLP-1 RA) should be maintained, unless adverse effects (including significant treatment burden) or contraindications are present. Use of sulfonylureas, meglitinides, and DPP-4 inhibitors should be limited or discontinued, as these medications do not have additional beneficial effects on cardiovascular, kidney, weight, or liver outcomes and (for sulfonylureas and meglitinides) increase risk of hypoglycemia and weight gain. Adjunctive use of pioglitazone may help to improve glycemia and reduce the amount of insulin needed, although potential side effects should be considered.

Once a basal-bolus insulin plan is initiated, dose titration is important, with adjustments made in both prandial and basal insulins based on blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (also known as pattern control or pattern management). In some people with type 2 diabetes with significant clinical complexity, multimorbidity, and/or treatment burden, it may become necessary to simplify or deintensify complex insulin plans to decrease risk of hypoglycemia and improve quality of life (see Section 13, "Older Adults").

Concentrated Insulins

Concentrated preparations may be more convenient (fewer injections to achieve goal dose) and comfortable (less volume to inject the desired dose and/or less injection effort) for individuals and may improve treatment plan engagement in those with insulin resistance who require large doses of insulin. Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. U-500 regular insulin has distinct pharmacokinetics with similar onset but a delayed, blunted, and prolonged peak effect and longer duration of action compared with U-100 regular insulin; thus, it has characteristics more like a premixed intermediate-acting (NPH) and regular insulin product and can be used as two or three daily injections (177,178). U-300 glargine and U-200 degludec are three and two times, respectively, as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action

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than U-100 glargine but modestly lower efficacy per unit administered (179–181). The U-200 formulations of insulin degludec, insulin lispro, and insulin lispro-aabc have pharmacokinetics similar to those of their U-100 counterparts (182–184). While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors. If U-500 regular insulin vials are prescribed, the prescription should be accompanied by a prescription for U-500 syringes to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulin is primarily administered via subcutaneous injection or infusion. Administration devices provide some additional variation in the subcutaneous delivery beyond vial and syringe versus insulin pen. Those devices include continuous insulin pumps (programmable or automated basal and bolus settings and fixed basal and bolus settings) and bolus-only insulin patch pump. In addition, prandial or correction insulin doses may be administered using inhaled human insulin. Inhaled insulin is available as monomers of regular human insulin; studies in individuals with type 1 diabetes suggest that inhaled insulin has pharmacokinetics similar to those of RAA (185). Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with the RAA insulin lispro as well as clinically meaningful A1C reductions and weight reductions compared with the RAA insulin aspart over 24 weeks (186–188). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 s [FEV_1]). Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in individuals who smoke or who recently stopped smoking. All individuals require spirometry (FEV_1) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

ADDITIONAL RECOMMENDATIONS FOR ALL INDIVIDUALS WITH DIABETES

Recommendations

9.27 Monitor for signs of overbasalization during insulin therapy, such as significant bedtime-to-morning or postprandial-to-preprandial glucose differential, occurrences of hypoglycemia (aware or unaware), and high glycemic variability. When overbasalization is suspected, a thorough reevaluation should occur promptly to further tailor therapy to the individual's needs. **E**

9.28 Glucagon should be prescribed for all individuals requiring intensive insulin therapy or at high risk for hypoglycemia. Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not require reconstitution are preferred. **B**

9.29 Routinely assess all people with diabetes for financial obstacles that could impede their diabetes management. Clinicians, members of the diabetes care team, and social services professionals should work collaboratively, as appropriate and feasible, to support these individuals by implementing strategies to reduce costs, thereby improving their access to evidence-based care. **E**

9.30 In adults with diabetes and cost-related barriers, consider use of lower-cost medications for glycemic management (i.e., metformin, sulfonylureas, thiazolidinediones, and human insulin) within the context of their risks for hypoglycemia, weight gain, cardiovascular and kidney events, and other adverse effects. **E**

Several key aspects of insulin management that are relevant to all people with diabetes requiring insulin therapy, including available formulations, insulin plans and delivery systems, administration technique, and overbasalization, were discussed earlier in this section. Additional considerations for glucose-lowering therapy that may be relevant to people with all types of diabetes include glucagon coprescription and affordability of diabetes therapies.

Glucagon

Due to the risk of hypoglycemia with insulin treatment, all individuals treated with insulin or who are at high risk for hypoglycemia should be prescribed glucagon. Individuals with diabetes who are prescribed glucagon and those in close contact with them should be educated on the use and administration of the individual's prescribed glucagon product. The glucagon product available to individuals may differ based on coverage and cost; however, products that do not require reconstitution are preferred for ease of administration (189,190). Clinicians should routinely review the individual's access to glucagon, as appropriate glucagon prescribing is low (191–193). See Section 6, "Glycemic Goals and Hypoglycemia," for additional information on hypoglycemia and glucagon in individuals with diabetes.

Medication Costs and Affordability

Costs for noninsulin and insulin diabetes medications have increased dramatically over the past two decades, and an increasing proportion of cost is now passed on to people with diabetes and their families (194). **Table 9.3** provides cost information for currently approved noninsulin therapies, while **Table 9.4** provides these data for insulin. Of note, prices listed are average wholesale prices (AWP) (195) and National Average Drug Acquisition Costs (NADAC) (196); these estimates allow for a comparison of drug prices but do not represent the actual costs to people with diabetes because they do not account for various discounts, rebates, and other price adjustments often involved in prescription sales that affect the actual cost incurred by the individual. Medication costs can be a major source of stress for people with diabetes and contribute to worse medication-taking behavior (197); cost-reducing strategies may improve medication-taking behavior in some cases (198).

Although caps on out-of-pocket costs for insulin have been implemented for individuals with Medicare and for individuals on some commercial health plans, and three major insulin manufacturers have capped costs at $35 per month per insulin (199–202) (see Section 1, "Improving Care and Promoting Health in Populations"), individuals with high-deductible health plans and those without insurance coverage can incur very high out-of-pocket expenses for glucose-lowering therapies. Moreover, no such caps exist for diabetes durable medical equipment (i.e., equipment for glucose monitoring and insulin administration) or for

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noninsulin medications. It is therefore essential to screen all people with diabetes for financial concerns and cost-related barriers to care and to engage members of the health care team, including pharmacists, certified diabetes care and education specialists, social workers, community health workers, community paramedics, and others, to identify cost-saving opportunities for medications, diabetes durable medical equipment, and glucagon (203).

SPECIAL CIRCUMSTANCES AND POPULATIONS

Recommendations

9.31a Use of compounded products that are not approved by the FDA is not recommended due to uncertainty about their content and resulting concerns about safety, quality, and effectiveness. **E**

9.31b If a glucose-lowering medication is unavailable (e.g., in shortage), it is recommended to switch to a different FDA-approved medication with similar efficacy, as clinically appropriate. **E**

9.31c Upon resolution of the unavailability (e.g., shortage), reassess the appropriateness of resuming the original FDA-approved medication. **E**

9.32a Individuals with diabetes of childbearing potential should be counseled on contraception options **A** and the impact of some glucose-lowering medications on contraception efficacy. **C**

9.32b A person-centered shared decision-making approach to preconception planning is essential for all individuals with diabetes and of childbearing potential. **A** Preconception planning should address attainment of glycemic goals, **A** the time frame for discontinuing noninsulin glucose-lowering medications, **E** and optimal glycemic management in preparation for pregnancy. **A**

9.33 Educate individuals with diabetes who are at risk for developing diabetic ketoacidosis and/or follow a ketogenic eating pattern and who are treated with SGLT inhibitors on the risks and signs of ketoacidosis and methods of risk mitigation management, and provide them with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate). **E**

Therapeutic Strategies With Medication Unavailability

Health care professionals and people with diabetes struggle when medication supplies are insufficient to meet the demand. Recent examples of such circumstances include recalls involving a number of metformin products and the marked increase in demand for agents from the GLP-1 RA and dual GIP and GLP-1 RA classes. The latter circumstance led to such a low level of availability that products were determined by the FDA to be in shortage (204). To assist with supply of medications during the time they are in shortage (as signaled by their inclusion on the FDA Drug Shortages Database), compounding pharmacies and outsourcing compounding facilities are allowed to make copies, or products that are essentially duplicates of the marketed FDA-approved product (205). A significant number of concerning reports regarding safety and efficacy of compounded incretin products have emerged, however, including using salt forms of the FDA-approved product's active ingredient that are not proven safe or effective for use in humans, incorporation of additional ingredients not clinically tested when mixed with incretin products (e.g., vitamin B12 and vitamin B6), products provided in nonstandard concentrations and doses and/or multidose vials and prefilled syringes not accompanied by education or labeling to mitigate administration errors, and the emergence of counterfeit products that pose significant risk to individuals taking these products (206–209). Due to safety, quality, and effectiveness concerns, use of non–FDA-approved compounded products is not recommended (210). Instead, consider switching to a different FDA-approved medication as clinically appropriate (211). Once the desired FDA-approved product becomes available, individuals should be reassessed to determine the appropriateness of resuming the product based on their current care needs, preferences, and priorities.

Care Considerations for Individuals of Childbearing Potential

The impact of glycemia during pregnancy is well understood; however, evidence for the safe use of noninsulin glucose-lowering medications is limited (see Section 15, "Management of Diabetes in Pregnancy"). Studies on the efficacy and safety of glucose-lowering medications exclude individuals who are pregnant and require individuals of childbearing potential to use one or two forms of contraception. It is recommended that individuals of childbearing potential use a form of contraception when also taking glucose-lowering medications with unknown risks, limited evidence on safety, or known risks during pregnancy, regardless of the individual's intention to become pregnant, as many pregnancies are unplanned. The options for contraception should be discussed with all individuals of childbearing potential with diabetes and should include information regarding the potential impact of glucose-lowering medications on the effectiveness of contraception. Medications that impact gastrointestinal emptying time (e.g., GLP-1 RAs or dual GIP and GLP-1 RA) may affect the absorption of orally administered medications, including oral contraception. The impact on gastric emptying with GLP-1 RAs and the dual GIP and GLP-1 RA is highest at initiation and with dosage increases and then diminishes with continued administration (212). Tirzepatide, the dual GIP and GLP-1 RA, was shown to impact the levels of oral contraception during the time of its highest impact on gastric emptying; the GLP-1 RAs may impact the levels of oral contraception as well but to a lesser extent than tirzepatide (213,214). Thus, individuals starting or increasing doses of tirzepatide who also take oral contraception should use a second form of contraception until the maintenance dose of tirzepatide is achieved and used for at least 4 weeks (215).

Preconception counseling should be part of the routine care of individuals with diabetes who have childbearing potential. Counseling should include the known benefits and risks of glucose-lowering medications as well as other medications (e.g., lipid-lowering and antihypertensive therapies) during pregnancy and recommendations for when changes in medications should occur prior to pregnancy (see Section 15, "Management of Diabetes in Pregnancy," for more information on preconception counseling and glucose-lowering treatment during pregnancy).

Therapeutic Strategies for Individuals Receiving Cancer Treatment

Hyperglycemia due to chemotherapy may either be transient (improving upon treatment cessation) or represent permanent

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Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound	Dosage strength/ product (if applicable)	Maximum approved daily dose†	Median AWP (min, max)*	Median NADAC (min, max)*
Biguanides	• Metformin	500 mg (ER)	2,000 mg	$89 ($5, $6,719)	$3 ($3, $79)
		850 mg (IR)	2,550 mg	$108 ($4, $189)	$2
		1,000 mg (IR)	2,000 mg	$87 ($3, $146)	$1
		1,000 mg (ER)	2,000 mg	$1,884 ($242, $7,214)	$26 ($21, $31)
		500 mg (Sol)	2,000 mg	$1,144 ($810, $1478)	$427
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	8 mg	$73 ($71, $198)	$2
	• Glipizide	10 mg (IR)	40 mg	$72 ($67, $91)	$5
		10 mg (XL/ER)	20 mg	$48 ($46, $48)	$8
	• Glyburide	6 mg (micronized)	12 mg	$54 ($48, $71)	$13
		5 mg	20 mg	$82 ($63, $432)	$7
Thiazolidinedione	• Pioglitazone	45 mg	45 mg	$348 ($7, $349)	$3
α-Glucosidase inhibitors	• Acarbose	100 mg	300 mg	$106 ($104, $378)	$20
	• Miglitol	100 mg	300 mg	$294 ($241, $346)	$320
Meglitinides	• Nateglinide	120 mg	360 mg	$155	$23
	• Repaglinide	2 mg	16 mg	$878 ($799, $897)	$26
DPP-4 inhibitors	• Alogliptin	25 mg	25 mg	$234	$145
	• Linagliptin	5 mg	5 mg	$630	$503
	• Saxagliptin	5 mg	5 mg	$524 ($523, $524)	$165
	• Sitagliptin	100 mg	100 mg	$588	$550
SGLT2 inhibitors	• Bexagliflozin	20 mg	20 mg	$47	NA
	• Canagliflozin	300 mg	300 mg	$718	$574
	• Dapagliflozin	10 mg	10 mg	$664	$352
	• Empagliflozin	25 mg	25 mg	$733	$586
	• Ertugliflozin	15 mg	15 mg	$428	$343
GLP-1 RAs	• Dulaglutide	4.5 mg pen	4.5 mg‡	$1,173	$941
	• Exenatide	10 mg pen	20 mg	$1,020	$818
	• Exenatide (ER)	2 mg pen	2 mg‡	$993	$1,101
	• Liraglutide	18 mg/3 mL pen	1.8 mg	$929	$1,077
	• Semaglutide	2 mg pen	2 mg‡	$1,162	$933
		14 mg (tablet)	14 mg	$1,162	$933
Dual GIP and GLP-1 RA	• Tirzepatide	15 mg pen	15 mg‡	$1,283	$1,030
Bile acid sequestrant	• Colesevelam	625 mg tabs	3.75 g	$692 ($674, $712)	$47
		3.75 g suspension	3.75 g	$674 ($673, $675)	$115
Dopamine-2 agonist	• Bromocriptine	0.8 mg	4.8 mg	$1,220	$981
Amylin mimetic	• Pramlintide	120 μg pen	120 μg§	$2,952	NA

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. AWP (195) and NADAC (196) prices are as of 1 July 2024. *Calculated for 30-day supply (AWP or NADAC unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. †Used to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. ‡Administered once weekly. §AWP and NADAC calculated based on 120 μg three times daily.

diabetes. Immune checkpoint inhibitors (ICIs) (agents that block programmed cell death protein 1 [PD-1] and programmed cell death protein ligand 1 [PD-L1]) suppress physiologic blocks on immune responses, which can result in autoimmune toxicities, including autoimmune diabetes (incidence approximately ≤1%). ICI-diabetes is an insulin-deficient phenotype that presents as acute severe hyperglycemia or DKA and appears to occur more abruptly than type 1 diabetes (216–218).

Alpelisib, a phosphatidylinositol-3-kinase (PI3K) inhibitor, frequently results in hyperglycemia by inhibiting PI3Kα, which systemically blocks the intracellular action of insulin, resulting in a transient state of insulin resistance and hyperglycemia (219). Hyperglycemia occurs early during therapy (median time of onset of about 2 weeks from initiation of alpelisib) with an incidence of ∼60% overall and typically resolves upon treatment cessation (220–222). Metformin is the first-line oral agent to treat alpelsib-induced hyperglycemia, and prophylactic initiation of metformin has been recommended for people with prediabetes receiving alpelsib (223). SGLT2 inhibitors and pioglitazone are appropriate second- or third-line agents, depending on side effect and clinical profiles, and may be used in combination with or without metformin. Insulin and sulfonylureas should be considered last-line agents, as insulin can reactivate the PI3K pathway, negating the effects of alpelisib (223,224).

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Table 9.4—Median cost of insulin products in the U.S. calculated as AWP and NADAC per 1,000 units of specified dosage form or product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting	• Aspart	U-100 vial	$87†	$70†
		U-100 cartridge	$107†	$86†
		U-100 prefilled pen	$112†	$90†
	• Aspart ("faster acting product")	U-100 vial	$347	$278
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Glulisine	U-100 vial	$102	$82
		U-100 prefilled pen	$132	$105
	• Inhaled insulin	Inhalation cartridges	$1,503	$1,298
	• Lispro	U-100 vial	$30†	$24†
		U-100 cartridge	$123	$98
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$263
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	$339
	• Lispro follow-on product	U-100 vial	$118	$94
		U-100 prefilled pen	$151	$121
Short-acting	• Human regular	U-100 vial	$58 ($54, $58)‡	$46 ($43, $58)‡
		U-100 prefilled pen	$73 ($54, $178)	$58
Intermediate-acting	• Human NPH	U-100 vial	$58 ($54, $58)‡	$45 ($43, $46)‡
		U-100 prefilled pen	$93 ($73, $113)	$74 ($58, $91)
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Degludec	U-100 vial	$142†	$114†
		U-100 prefilled pen	$142†	$114†
		U-200 prefilled pen	$85†	$114†
	• Glargine	U-100 vial	$77	$109†
		U-100 prefilled pen	$77	$109†
		U-300 prefilled pen	$152†	$122†
	• Glargine biosimilar/follow-on products	U-100 vial	$118 ($76,† $323)	$61†
		U-100 prefilled pen	$118 ($74,† $323)	$59 ($59,† $209)
Premixed insulin products	• Aspart 70/30	U-100 vial	$87†‡	$69†‡
		U-100 prefilled pen	$112†‡	$90†‡
	• Lispro 50/50	U-100 vial	$102	NA
		U-100 prefilled pen	$127	$102
	• Lispro 75/25	U-100 vial	$102	$82
		U-100 prefilled pen	$127†	$102†
	• NPH/regular 70/30	U-100 vial	$58 ($54, $58)	$45 ($43, $46)
		U-100 prefilled pen	$73 ($73, $113)‡	$74 ($58, $90)‡
Premixed insulin/GLP-1 RA products	• Degludec/liraglutide	100/3.6 mg prefilled pen	$1,037	$791
	• Glargine/lixisenatide	100/33 mg prefilled pen	$713	$570

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP (195) and NADAC (196) prices as of 1 July 2024. *AWP or NADAC calculated as in **Table 9.3**. †Unbranded product prices used when available. ‡AWP and NADAC data presented do not include human insulins (approximately $25/vial or $43/box of 5 pens) or select analog insulins (approximately $73/vial or $86/box of 5 pens) available at Walmart; median listed alone when only one product and/or price.

mTOR kinase inhibitors, including everilomus, cause hyperglycemia by interfering with insulin signaling, leading to impaired insulin secretion and increased insulin resistance. Metformin is the first-line treatment of hyperglycemia secondary to mTOR inhibitor treatment, with insulin and other noninsulin treatments added in a stepwise fashion dependent on glucose level (225).

Therapeutic Strategies for Individuals With Other Types of Diabetes

Individuals with pancreatogenic diabetes may require early insulin initiation to achieve and maintain glycemic goals. In

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individuals with a history of pancreatitis, use of incretin medications (i.e., GLP-1 RAs, GIP and GLP-1 RA, and DPP-4 inhibitors) should be avoided (see Section 2, "Diagnosis and Classification of Diabetes"). Individuals with cystic fibrosis–related diabetes should be treated with insulin therapy; insulin pump therapy, including automated insulin delivery systems, should be considered when appropriate (226).

There are limited data to inform the optimal pharmacologic management of posttransplant diabetes (227) (see Section 2, "Diagnosis and Classification of Diabetes"). While immediately posttransplant many individuals require insulin therapy, noninsulin therapies can be used for long-term management. Studies of metformin, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 RAs, and pioglitazone in individuals who have undergone kidney, heart, or liver transplantation have demonstrated effectiveness and safety but are limited by small sample sizes, short follow-up, and risk of bias due to retrospective or single-arm prospective designs (228). Metformin should be used with caution; it should not be initiated if eGFR is <45 mL/min/1.73 m^2, it should be stopped with eGFR ≥ 30 mL/min/1.73 m^2, and it should not be used in the setting of clinical instability due to concerns for acute kidney injury and lactic acidosis. Metformin use may be associated with lower risks of cardiac allograph vasculopathy after heart transplantation (229) and all-cause, malignancy-related, and infection-related mortality after kidney transplantation (230). GLP-1 RA therapy may be preferred for many individuals due to the demonstrated benefit of GLP-1 RAs on cardiovascular, kidney, weight, and liver outcomes. Studies have not found evidence of drug interaction with immunosuppression, including finding no changes in dosing or toxicity (231–233). SGLT2 inhibitors may be similarly preferred for individuals with ASCVD, HF, and CKD and appear to be safe and effective in posttransplantation diabetes. However, there is increased risk of genitourinary tract infection, which is a concern in individuals receiving immunosuppression and in those who have undergone kidney transplantation.

Individuals with maturity-onset diabetes of the young due to *HNF1A* and *HNF4A* mutations can be treated with low-dose sulfonylurea therapy but may ultimately require insulin therapy (234) (see Section 2, "Diagnosis and Classification of Diabetes") (**Table 2.7**). For those with *HNF1A* mutations, addition of a DPP-4 inhibitor to the sulfonylurea may help improve glycemic variability and attainment of glycemic goals (235). Individuals with neonatal diabetes due to *KCNJ22* and *ABCC8* mutations can be treated with high-dose sulfonylureas, while those with *INS*, *GATA6*, *EIF2AK3*, and *FOXP3* mutations require insulin therapy (234).

SGLT Inhibition and Risk of Ketosis

Individuals with type 1 diabetes (84,236) and insulin-deficient type 2 diabetes are at increased risk for DKA with SGLT inhibitor therapy. SGLT inhibitor–associated DKA occurs in approximately 4% of people with type 1 diabetes; the risk can be 5–17 times higher than that in people with T1D not treated with SGLT inhibitors (237). It is important to note that SGLT2 inhibitors are not approved for use in people with type 1 diabetes. In contrast, DKA is uncommon in people with type 2 diabetes treated with SGLT inhibitors, with an estimated incidence of 0.6–4.9 events per 1,000 person-years (238). Risk factors for DKA in individuals with either type 1 or type 2 diabetes treated with SGLT inhibitors include very-low-carbohydrate diets, prolonged fasting, dehydration, excessive alcohol intake, and other common precipitating factors (84,236). Up to a third of people treated with SGLT2 inhibitors who developed DKA present with glucose levels <200 mg/dL (11.1 mmol/L) (239), and in one study 71% presented with glucose levels ≤ 250 mg/dL (13.9 mmol/L) (240); therefore, it is important to educate at-risk individuals about the signs and symptoms of DKA and DKA mitigation and management and to prescribe accurate tools for ketone measurement. Individuals who have experienced DKA should not be treated with SGLT inhibition. Additional guidance on DKA risk mitigation is available in Section 6, "Glycemic Goals and Hypoglycemia."

References

1. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383
2. Lachin JM, Bebu I, Nathan DM, DCCT/EDIC Research Group. The beneficial effects of earlier versus later implementation of intensive therapy in type 1 diabetes. Diabetes Care 2021;44:2225–2230
3. Lachin JM, Nathan DM, DCCT/EDIC Research Group. Understanding metabolic memory: the prolonged influence of glycemia during the Diabetes Control and Complications Trial (DCCT) on future risks of complications during the study of the Epidemiology of Diabetes Interventions and Complications (EDIC). Diabetes Care 2021;44:2216–2224
4. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021;44:2589–2625
5. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ 2014;349:g5459
6. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to neutral protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442–449
7. Little S, Shaw J, Home P. Hypoglycemia rates with basal insulin analogs. Diabetes Technol Ther 2011;13(Suppl 1):S53–S64
8. Aronson R, Biester T, Leohr J, et al. Ultra rapid lispro showed greater reduction in postprandial glucose versus Humalog in children, adolescents and adults with type 1 diabetes mellitus. Diabetes Obes Metab 2023;25:1964–1972
9. Heise T, Pieber TR, Danne T, Erichsen L, Haahr H. A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes. Clin Pharmacokinet 2017;56:551–559
10. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC, Bregman DB; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 2015;38:2266–2273
11. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). Diabetes Care 2017;40:943–950
12. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. Diabetes Obes Metab 2020;22:1799–1807
13. Lane W, Bailey TS, Gerety G, et al.; SWITCH 1. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. JAMA 2017;318:33–44
14. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care 2015;38:2217–2225
15. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336–347
16. Speight J, Choudhary P, Wilmot EG, et al. Impact of glycaemic technologies on quality of

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life and related outcomes in adults with type 1 diabetes: a narrative review. Diabet Med 2023; 40:e14944
17. Barnard KD, Skinner TC. Cross-sectional study into quality of life issues surrounding insulin pump use in type 1 diabetes. Practical Diabetes International 2008;25:194–200
18. Mulinacci G, Alonso GT, Snell-Bergeon JK, Shah VN. Glycemic outcomes with early initiation of continuous glucose monitoring system in recently diagnosed patients with type 1 diabetes. Diabetes Technol Ther 2019;21:6–10
19. Elbalshy M, Haszard J, Smith H, et al. Effect of divergent continuous glucose monitoring technologies on glycaemic control in type 1 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials. Diabet Med 2022;39:e14854
20. Champakanath A, Akturk HK, Alonso GT, Snell-Bergeon JK, Shah VN. Continuous glucose monitoring initiation within first year of type 1 diabetes diagnosis is associated with improved glycemic outcomes: 7-year follow-up study. Diabetes Care 2022;45:750–753
21. Weinstock RS, Xing D, Maahs DM, et al.; T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab 2013;98:3411–3419
22. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476
23. Polonsky WH, Hessler D, Ruedy KJ, Beck RW; DIAMOND Study Group. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND randomized clinical trial. Diabetes Care 2017;40:736–741
24. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
25. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. Diabetes Care 2018;41:2155–2161
26. Phillip M, Nimri R, Bergenstal RM, et al. Consensus recommendations for the use of automated insulin delivery technologies in clinical practice. Endocr Rev 2023;44:254–280
27. Peacock S, Frizelle I, Hussain S. A systematic review of commercial hybrid closed-loop automated insulin delivery systems. Diabetes Ther 2023;14: 839–855
28. Choudhary P, Kolassa R, Keuthage W, et al.; ADAPT Study Group. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. Lancet Diabetes Endocrinol 2022; 10:720–731
29. Arunachalum S, Velado K, Vigersky RA, Cordero TL. Glycemic outcomes during real-world hybrid closed-loop system use by individuals with type 1 diabetes in the United States. J Diabetes Sci Technol 2023;17:951–958
30. Garg SK, Grunberger G, Weinstock R, et al.; Adult and Pediatric MiniMed HCL Outcomes 6-Month RCT: HCL Versus CSII Control Study Group. Improved glycemia with hybrid closed-loop versus continuous subcutaneous insulin infusion therapy: results from a randomized controlled trial. Diabetes Technol Ther 2023;25:1–12
31. Russell SJ, Beck RW, Damiano ER, et al.; Bionic Pancreas Research Group. Multicenter, randomized trial of a bionic pancreas in type 1 diabetes. N Engl J Med 2022;387:1161–1172
32. Burnside MJ, Lewis DM, Crocket HR, et al. Open-source automated insulin delivery in type 1 diabetes. N Engl J Med 2022;387:869–881
33. Burnside MJ, Lewis DM, Crocket HR, et al. Extended use of an open-source automated insulin delivery system in children and adults with type 1 diabetes: the 24-week continuation phase following the CREATE randomized controlled trial. Diabetes Technol Ther 2023;25:250–259
34. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717
35. Collyns OJ, Meier RA, Betts ZL, et al. Improved glycemic outcomes with Medtronic MiniMed advanced hybrid closed-loop delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. Diabetes Care 2021;44:969–975
36. Brown SA, Beck RW, Raghinaru D, et al.; iDCL Trial Research Group. Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial. Diabetes Care 2020;43:1822–1828
37. Breton MD, Kovatchev BP. One year real-world use of the Control-IQ advanced hybrid closed-loop technology. Diabetes Technol Ther 2021;23:601–608
38. Lepore G, Rossini A, Bellante R, et al. Switching to the MiniMed 780G system achieves clinical targets for CGM in adults with type 1 diabetes regardless of previous insulin strategy and baseline glucose control. Acta Diabetol 2022;59: 1309–1315
39. Matejko B, Juza A, Kieć-Wilk B, et al. Transitioning of people with type 1 diabetes from multiple daily injections and self-monitoring of blood glucose directly to MiniMed 780G advanced hybrid closed-loop system: a two-center, randomized, controlled study. Diabetes Care 2022; 45:2628–2635
40. Isganaitis E, Raghinaru D, Ambler-Osborn L, et al.; iDCL Trial Research Group. Closed-loop insulin therapy improves glycemic control in adolescents and young adults: outcomes from the international diabetes closed-loop trial. Diabetes Technol Ther 2021;23:342–349
41. Forlenza GP, Carlson AL, Galindo RJ, et al. Real-world evidence supporting Tandem Control-IQ hybrid closed-loop success in the Medicare and Medicaid type 1 and type 2 diabetes populations. Diabetes Technol Ther 2022;24:814–823
42. Pease A, Zomer E, Liew D, et al. Cost-effectiveness analysis of a hybrid closed-loop system versus multiple daily injections and capillary glucose testing for adults with type 1 diabetes. Diabetes Technol Ther 2020;22:812–821
43. Lal RA, Maahs DM. Optimizing basal insulin dosing. J Pediatr 2019;215:7–8
44. Mitsui Y, Kuroda A, Ishizu M, et al. Basal insulin requirement in patients with type 1 diabetes depends on the age and body mass index. J Diabetes Investig 2022;13:292–298
45. Castellano E, Attanasio R, Giagulli VA, et al.; Associazione Medici Endocrinologi (AME). The basal to total insulin ratio in outpatients with diabetes on basal-bolus regimen. J Diabetes Metab Disord 2018;17:393–399
46. Matejko B, Kukułka A, Kieć-Wilk B, Stąpór A, Klupa T, Malecki MT. Basal insulin dose in adults with type 1 diabetes mellitus on insulin pumps in real-life clinical practice: a single-center experience. Adv Med 2018;2018:1473160
47. Cengiz E, Danne T, Ahmad T, et al. ISPAD Clinical Practice Consensus Guidelines 2022: insulin treatment in children and adolescents with diabetes. Pediatr Diabetes 2022;23:1277–1296
48. King AB. Mean basal insulin dose is 0.2 U/kg/d at near normal glycaemia for type 1 or 2 diabetes on continuous subcutaneous insulin infusion or once-nightly basal insulin. Diabetes Obes Metab 2021;23:866–869
49. Peters AL, Lafell L. *The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook.* American Diabetes Association, 2013
50. Srinivasan S, Craig ME, Beeney L, et al. An ambulatory stabilisation program for children with newly diagnosed type 1 diabetes. Med J Aust 2004;180:277–280
51. Lemieux L, Crawford S, Pacaud D. Starting subcutaneous insulin doses in a paediatric population with newly diagnosed type 1 diabetes. Paediatr Child Health 2010;15:357–362
52. Chiang JL, Kirkman MS, Laffel LMB, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2034–2054
53. Sämann A, Mühlhauser I, Bender R, Hunger-Dathe W, Kloos C, Müller UA. Flexible intensive insulin therapy in adults with type 1 diabetes and high risk for severe hypoglycemia and diabetic ketoacidosis. Diabetes Care 2006;29:2196–2199
54. Builes-Montaño CE, Ortiz-Cano NA, Ramirez-Rincón A, Rojas-Henao NA. Efficacy and safety of carbohydrate counting versus other forms of dietary advice in patients with type 1 diabetes mellitus: a systematic review and meta-analysis of randomised clinical trials. J Hum Nutr Diet 2022;35:1030–1042
55. Al Balwi R, Al Madani W, Al Ghamdi A. Efficacy of insulin dosing algorithms for high-fat high-protein mixed meals to control postprandial glycemic excursions in people living with type 1 diabetes: A systematic review and meta-analysis. Pediatr Diabetes 2022;23:1635–1646
56. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose Adjustment For Normal Eating (DAFNE) randomised controlled trial. BMJ 2002;325:746
57. Hopkins D, Lawrence I, Mansell P, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 2012;35:1638–1642
58. Speight J, Amiel SA, Bradley C, et al. Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled type 1 diabetes. Diabetes Res Clin Pract 2010;89:22–29

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59. Bruttomesso D, Boscari F, Lepore G, et al. A "slide rule" to adjust insulin dose using trend arrows in adults with type 1 diabetes: test in silico and in real life. Diabetes Ther 2021;12:1313–1324
60. Aleppo G, Laffel LM, Ahmann AJ, et al. A practical approach to using trend arrows on the Dexcom G5 CGM system for the management of adults with diabetes. J Endocr Soc 2017;1:1445–1460
61. Buckingham B, Xing D, Weinzimer S, et al.; Diabetes Research In Children Network (DirecNet) Study Group. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). Pediatr Diabetes 2008;9:142–147
62. Parise M, Di Molfetta S, Graziano RT, et al. A head-to-head comparison of two algorithms for adjusting mealtime insulin doses based on CGM trend arrows in adult patients with type 1 diabetes: results from an exploratory study. Int J Environ Res Public Health 2023;20:3945
63. Petrovski G, Campbell J, Pasha M, et al. Simplified meal announcement versus precise carbohydrate counting in adolescents with type 1 diabetes using the MiniMed 780G advanced hybrid closed loop system: a randomized controlled trial comparing glucose control. Diabetes Care 2023;46:544–550
64. Turrin KB, Trujillo JM. Effects of diabetes numeracy on glycemic control and diabetes self-management behaviors in patients on insulin pump therapy. Diabetes Ther 2019;10:1337–1346
65. White RO, Wolff K, Cavanaugh KL, Rothman R. Addressing health literacy and numeracy to improve diabetes education and care. Diabetes Spectr 2010;23:238–243
66. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. Mayo Clin Proc 2016;91:1231–1255
67. Bergenstal RM, Strock ES, Peremislov D, Gibney MA, Parvu V, Hirsch LJ. Safety and efficacy of insulin therapy delivered via a 4mm pen needle in obese patients with diabetes. Mayo Clin Proc 2015;90:329–338
68. Qiao Y-C, Ling W, Pan Y-H, et al. Efficacy and safety of pramlintide injection adjunct to insulin therapy in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. Oncotarget 2017;8:66504–66515
69. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev 2018;34:e2983
70. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:597–609
71. Mathieu C, Zinman B, Hemmingsson JU, et al.; ADJUNCT ONE Investigators. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care 2016;39:1702–1710
72. Ahrén B, Hirsch IB, Pieber TR, et al.; ADJUNCT TWO Investigators. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care 2016;39:1693–1701
73. von Herrath M, Bain SC, Bode B, et al.; Anti-IL-21–Liraglutide Study Group Investigators and Contributors. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2021;9:212–224
74. Garg SK, Kaur G, Haider Z, Rodriquez E, Beatson C, Snell-Bergeon J. Efficacy of semaglutide in overweight and obese patients with type 1 diabetes. Diabetes Technol Ther 2024;26:184–189
75. Garg SK, Akturk HK, Kaur G, Beatson C, Snell-Bergeon J. Efficacy and safety of tirzepatide in overweight and obese adult patients with type 1 diabetes. Diabetes Technol Ther 2024;26:367–374
76. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. Type 1 Diabetes Impacts of Semaglutide on Cardiovascular Outcomes (T1-DISCO) (NCT05819138). Accessed 23 August 2024. Available from https://clinicaltrials.gov/study/NCT05819138?tab=results
77. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. ADJUnct Semaglutide Treatment in Type 1 Diabetes (ADJUST-T1D) (NCT05537233). Accessed 23 August 2024. Available from https://clinicaltrials.gov/study/NCT05537233
78. Rao L, Ren C, Luo S, Huang C, Li X. Sodium-glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: meta-analysis of randomized controlled trials. Acta Diabetol 2021;58:869–880
79. Li M, Liu Z, Yang X, et al. The effect of sodium-glucose cotransporter 2 inhibitors as an adjunct to insulin in patients with type 1 diabetes assessed by continuous glucose monitoring: a systematic review and meta-analysis. J Diabetes Complications 2023;37:108632
80. Chen M-B, Xu R-J, Zheng Q-H, Zheng X-W, Wang H. Efficacy and safety of sotagliflozin adjuvant therapy for type 1 diabetes mellitus: a systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e20875
81. U.S. Food and Drug Administration. FDA Introductory Remarks: January 17, 2019: Endocrinologic and Metabolic Drugs Advisory Committee Meeting. 2019. Accessed 23 August 2024. Available from https://wayback.archive-it.org/7993/20190207212714/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM629782.pdf
82. Bhatt DL, Szarek M, Steg PG, et al.; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117–128
83. Bhatt DL, Szarek M, Pitt B, et al.; SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2021;384:129–139
84. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care 2019;42:1147–1154
85. Lachin JM, McGee P, Palmer JP, DCCT/EDIC Research Group. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes 2014;63:739–748
86. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. BMJ 2017;357:j1321
87. U.S. Food & Drug Administration. Lantidra. Accessed 15 September 2024. Available from https://www.fda.gov/vaccines-blood-biologics/lantidra
88. Geta ET, Terefa DR, Hailu WB, et al. Effectiveness of shared decision-making for glycaemic control among type 2 diabetes mellitus adult patients: a systematic review and meta-analysis. PLoS One 2024;19:e0306296
89. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753–2786
90. Lingvay I, Sumithran P, Cohen RV, Le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet 2022;399:394–405
91. Wing RR, Lang W, Wadden TA, et al.; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481–1486
92. Adler AI, Coleman RL, Leal J, Whiteley WN, Clarke P, Holman RR. Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). Lancet 2024;404:145–155
93. Kunutsor SK, Balasubramanian VG, Zaccardi F, et al. Glycaemic control and macrovascular and microvascular outcomes: a systematic review and meta-analysis of trials investigating intensive glucose-lowering strategies in people with type 2 diabetes. Diabetes Obes Metab 2024;26:2069–2081
94. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
95. Bahardoust M, Mousavi S, Yariali M, et al. Effect of metformin (vs. placebo or sulfonylurea) on all-cause and cardiovascular mortality and incident cardiovascular events in patients with diabetes: an umbrella review of systematic reviews with meta-analysis. J Diabetes Metab Disord 2024;23:27–38
96. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751
97. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369
98. U.S. Food & Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Accessed 23 August 2024. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain

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99. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med 2003;163:2594–2602
100. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;2010: CD002967
101. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431–1437
102. Out M, Kooy A, Lehert P, Schalkwijk CA, Stehouwer CDA. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: post hoc analysis of a randomized controlled 4.3year trial. J Diabetes Complications 2018;32: 171–178
103. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016; 101:1754–1761
104. Frías JP, Davies MJ, Rosenstock J, et al.; SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 2021;385:503–515
105. Sorli C, Harashima S-I, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 2017;5:251–260
106. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med 2020;173:278–286
107. Kahn SE, Haffner SM, Heise MA, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443
108. Nathan DM, Lachin JM, Balasubramanyam A, et al.; GRADE Study Research Group. Glycemia reduction in type 2 diabetes–glycemic outcomes. N Engl J Med 2022;387:1063–1074
109. Babu A, Mehta A, Guerrero P, et al. Safe and simple emergency department discharge therapy for patients with type 2 diabetes mellitus and severe hyperglycemia. Endocr Pract 2009; 15:696–704
110. Buse JB, Peters A, Russell-Jones D, et al. Is insulin the most effective injectable antihyperglycaemic therapy? Diabetes Obes Metab 2015;17: 145–151
111. D'Alessio D, Häring H-U, Charbonnel B, et al.; EAGLE Investigators. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabetes Obes Metab 2015;17:170–178
112. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care 2016;39(Suppl 2):S137–S145
113. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. Diabetes Obes Metab 2015;17:268–275
114. Cai X, Gao X, Yang W, Han X, Ji L. Efficacy and safety of initial combination therapy in treatment-naïve type 2 diabetes patients: a systematic review and meta-analysis. Diabetes Ther 2018;9:1995–2014
115. Aroda VR, González-Galvez G, Grøn R, et al. Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:596–605
116. Khunti K, Davies MJ. Clinical inertia–time to reappraise the terminology? Prim Care Diabetes 2017;11:105–106
117. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011; 154:602–613
118. Maloney A, Rosenstock J, Fonseca V. A model-based meta-analysis of 24 antihyperglycemic drugs for type 2 diabetes: comparison of treatment effects at therapeutic doses. Clin Pharmacol Ther 2019;105:1213–1223
119. Lajthia E, Bucheit JD, Nadpara PA, et al. Combination therapy with once-weekly glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a case series. Pharm Pract (Granada) 2019;17:1588
120. Violante R, Oliveira JHA, Yoon K-H, et al. A randomized non-inferiority study comparing the addition of exenatide twice daily to sitagliptin or switching from sitagliptin to exenatide twice daily in patients with type 2 diabetes experiencing inadequate glycaemic control on metformin and sitagliptin. Diabet Med 2012;29:e417–e424
121. Nauck MA, Kahle M, Baranov O, Deacon CF, Holst JJ. Addition of a dipeptidyl peptidase-4 inhibitor, sitagliptin, to ongoing therapy with the glucagon-like peptide-1 receptor agonist liraglutide: a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes Metab 2017;19:200–207
122. Pratley R, Amod A, Hoff ST, et al.; PIONEER 4 Investigators. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019;394:39–50
123. Del Prato S, Kahn SE, Pavo I, et al.; SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet 2021;398:1811–1824
124. Singh S, Wright EE, Kwan AYM, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2017;19:228–238
125. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. Diabetes Metab Syndr Obes 2017;10: 123–139
126. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. Diabetes Obes Metab 2017;19:216–227
127. Giorgino F, Benroubi M, Sun J-H, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Diabetes Care 2015; 38:2241–2249
128. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017;5:355–366
129. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care 2013;36:1368–1376
130. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 2010;375:2234–2243
131. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. JAMA 2022;327:534–545
132. McCoy RG, Lipska KJ, Van Houten HK, Shah ND. Association of cumulative multimorbidity, glycemic control, and medication use with hypoglycemia-related emergency department visits and hospitalizations among adults with diabetes. JAMA Netw Open 2020;3:e1919099
133. Nathan DM, Lachin JM, Bebu I, et al.; GRADE Study Research Group. Glycemia reduction in type 2 diabetes–microvascular and cardiovascular outcomes. N Engl J Med 2022;387:1075–1088
134. McCoy RG, Herrin J, Swarna KS, et al. Effectiveness of glucose-lowering medications on cardiovascular outcomes in patients with type 2 diabetes at moderate cardiovascular risk. Nat Cardiovasc Res 2024;3:431–440
135. Berg DD, Wiviott SD, Scirica BM, et al. Heart failure risk stratification and efficacy of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes mellitus. Circulation 2019; 140:1569–1577
136. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102:S1–S127
137. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7:776–785
138. Perkovic V, Tuttle KR, Rossing P, et al.; FLOW Trial Committees and Investigators. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024; 391:109–121
139. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2

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diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–158
140. Reyes-Farias CI, Reategui-Diaz M, Romani-Romani F, Prokop L. The effect of sodium-glucose cotransporter 2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes mellitus on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS One 2023;18:e0295059
141. Herrington WG, Staplin N, Wanner C, et al.; Empa-Kidney Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388:117–127
142. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
143. Dagogo-Jack S, Pratley RE, Cherney DZI, et al. Glycemic efficacy and safety of the SGLT2 inhibitor ertugliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease: an analysis from the VERTIS CV randomized trial. BMJ Open Diabetes Res Care 2021;9:e002484
144. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. Kidney Int 2018;93:231–244
145. Wexler DJ, de Boer IH, Ghosh A, et al.; GRADE Research Group. Comparative effects of glucose-lowering medications on kidney outcomes in type 2 diabetes: the GRADE randomized clinical trial. JAMA Intern Med 2023;183:705–714
146. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307
147. Cusi K, Orsak B, Bril F, Xu et al. Liraglutide or insulin glargine treatments improves hepatic fat in obese patients with type 2 diabetes and nonalcoholic fatty liver disease in twenty-six weeks: a randomized placebo-controlled trial. Diabetes Res Clin Pract 2020;170:108487
148. Flint A, Andersen G, Hockings P, et al. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. Aliment Pharmacol Ther 2021;54:1150–1161
149. Bizino MB, Jazet IM, de Heer P, et al. Placebo-controlled randomised trial with liraglutide on magnetic resonance endpoints in individuals with type 2 diabetes: a pre-specified secondary study on ectopic fat accumulation. Diabetologia 2020;63:65–74
150. Newsome PN, Buchholtz K, Cusi K, et al.; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113–1124
151. Loomba R, Hartman ML, Lawitz EJ, et al.; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299–310
152. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol 2022;10:393–406
153. Armstrong MJ, Gaunt P, Aithal GP, et al.; LEAN Trial Team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–690
154. Sathyanarayana P, Jogi M, Muthupillai R, Krishnamurthy R, Samson SL, Bajaj M. Effects of combined exenatide and pioglitazone therapy on hepatic fat content in type 2 diabetes. Obesity (Silver Spring) 2011;19:2310–2315
155. Abdul-Ghani M, Migahid O, Megahed A, DeFronzo RA, Al-Ozairi E, Jayyousi A. Combination therapy with pioglitazone/exenatide improves beta-cell function and produces superior glycaemic control compared with basal/bolus insulin in poorly controlled type 2 diabetes: a 3-year follow-up of the Qatar study. Diabetes Obes Metab 2020;22:2287–2294
156. Lavynenko O, Abdul-Ghani M, Alatrach M, et al. Combination therapy with pioglitazone/exenatide/metformin reduces the prevalence of hepatic fibrosis and steatosis: the efficacy and durability of initial combination therapy for type 2 diabetes (EDICT). Diabetes Obes Metab 2022;24:899–907
157. Garvey WT, Frias JP, Jastreboff AM, et al.; SURMOUNT-2 Investigators. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2023;402:613–626
158. Davies M, Færch L, Jeppesen OK, et al.; STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971–984
159. Bonora E, Frias JP, Tinahones FJ, et al. Effect of dulaglutide 3.0 and 4.5 mg on weight in patients with type 2 diabetes: exploratory analyses of AWARD-11. Diabetes Obes Metab 2021;23:2242–2250
160. Davies MJ, Bergenstal R, Bode B, et al.; NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314:687–699
161. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care 2018;41:258–266
162. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes–5-year outcomes. N Engl J Med 2017;376:641–651
163. Blonde L, Merilainen M, Karwe V, Raskin P, TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets–the TITRATE study. Diabetes Obes Metab 2009;11:623–631
164. Porcellati F, Lucidi P, Cioli P, et al. Pharmacokinetics and pharmacodynamics of insulin glargine given in the evening as compared with in the morning in type 2 diabetes. Diabetes Care 2015;38:503–512
165. Wang Z, Hedrington MS, Gogitidze Joy N, et al. Dose-response effects of insulin glargine in type 2 diabetes. Diabetes Care 2010;33:1555–1560
166. Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K. (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 2020;11:Cd005613
167. Mannucci E, Caiulo C, Naletto L, Madama G, Monami M. Efficacy and safety of different basal and prandial insulin analogues for the treatment of type 2 diabetes: a network meta-analysis of randomized controlled trials. Endocrine 2021;74:508–517
168. Russell-Jones D, Gall M-A, Niemeyer M, Diamant M, Del Prato S. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: a meta-analysis of seven clinical trials. Nutr Metab Cardiovasc Dis 2015;25:898–905
169. Mehta R, Goldenberg R, Katselnik D, Kuritzky L. Practical guidance on the initiation, titration, and switching of basal insulins: a narrative review for primary care. Ann Med 2021;53:998–1009
170. Cowart K. Overbasalization: addressing hesitancy in treatment intensification beyond basal insulin. Clin Diabetes 2020;38:304–310
171. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care 2017;40:614–624
172. Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F. GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev 2019;35:e3082
173. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DHW. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014;2:30–37
174. McCall AL. Insulin therapy and hypoglycemia. Endocrinol Metab Clin North Am 2012;41:57–87
175. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. Diabetes Obes Metab 2009;11:53–59
176. Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. J Diabetes 2013;5:482–491
177. de la Peña A, Riddle M, Morrow LA, et al. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. Diabetes Care 2011;34:2496–2501
178. Wysham C, Hood RC, Warren ML, Wang T, Morwick TM, Jackson JA. Effect of total daily dose on efficacy, dosing, and safety of 2 dose titration regimens of human regular U500 insulin in severely insulin-resistant patients with type 2 diabetes. Endocr Pract 2016;22:653–665
179. Becker RHA, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 units · mL-1 provides a more even activity profile and prolonged glycemic control at steady state

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compared with insulin glargine 100 units · mL-1. Diabetes Care 2015;38:637–643
180. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab 2015; 17:835–842
181. Yki-Järvinen H, Bergenstal R, Ziemen M, et al.; EDITION 2 Study Investigators. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care 2014;37:3235–3243
182. Korsatko S, Deller S, Koehler G, et al. A comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. Clin Drug Investig 2013;33:515–521
183. de la Peña A, Seger M, Soon D, et al. Bioequivalence and comparative pharmacodynamics of insulin lispro 200 U/mL relative to insulin lispro (Humalog) 100 U/mL. Clin Pharmacol Drug Dev 2016;5:69–75
184. Gentile S, Fusco A, Colarusso S, et al. A randomized, open-label, comparative, crossover trial on preference, efficacy, and safety profiles of lispro insulin U-100 versus concentrated lispro insulin U-200 in patients with type 2 diabetes mellitus: a possible contribution to greater treatment adherence. Expert Opin Drug Saf 2018; 17:445–450
185. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254–2264
186. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. Diabetes Technol Ther 2018;20:639–647
187. Hoogwerf BJ, Pantalone KM, Basina M, Jones MC, Grant M, Kendall DM. Results of a 24-week trial of technosphere insulin versus insulin aspart in type 2 diabetes. Endocr Pract 2021;27:38–43
188. Grant M, Heise T, Baughman R. Comparison of pharmacokinetics and pharmacodynamics of inhaled technosphere insulin and subcutaneous insulin lispro in the treatment of type 1 diabetes mellitus. Clin Pharmacokinet 2022;61:413–422
189. Valentine V, Newswanger B, Prestrelski S, Andre AD, Garibaldi M. Human factors usability and validation studies of a glucagon autoinjector in a simulated severe hypoglycemia rescue situation. Diabetes Technol Ther 2019;21:522–530
190. Settles JA, Gerety GF, Spaepen E, Suico JG, Child CJ. Nasal glucagon delivery is more successful than injectable delivery: a simulated severe hypoglycemia rescue. Endocr Pract 2020; 26:407–415
191. Herges JR, Galindo RJ, Neumiller JJ, Heien HC, Umpierrez GE, McCoy RG. Glucagon prescribing and costs among U.S. adults with diabetes, 2011-2021. Diabetes Care 2023;46:620–627
192. Kahn PA, Liu S, McCoy R, Gabbay RA, Lipska K. Glucagon use by U.S. adults with type 1 and type 2 diabetes. J Diabetes Complications 2021; 35:107882
193. Benning TJ, Heien HC, Herges JR, Creo AL, Al Nofal A, McCoy RG. Glucagon fill rates and cost among children and adolescents with type 1 diabetes in the United States, 2011-2021. Diabetes Res Clin Pract 2023;206:111026
194. Riddle MC, Herman WH. The cost of diabetes care-an elephant in the room. Diabetes Care 2018;41:929–932
195. Merative. Redbook (electronic version). Accessed 1 July 2024. Available from https://www.micromedexsolutions.com
196. Data.Medicaid.gov. NADAC (National Average Drug Acquisition Cost). Accessed 1 July 2024. Available from https://healthdata.gov/dataset/NADAC-National-Average-Drug-Acquisition-Cost-2024/3tha-57c6/about_data
197. Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. Diabetes Res Clin Pract 2018; 143:24–33
198. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey. Med Care 2016;54:796–803
199. Centers for Medicare & Medicaid Services. Part D Senior Savings Model. Accessed 23 August 2024. Available from https://www.cms.gov/priorities/innovation/innovation-models/part-d-savings-model
200. Library of Congress. H.R.5376–Inflation Reduction Act of 2022. Accessed 23 August 2024. Available from https://www.congress.gov/bill/117th-congress/house-bill/5376
201. American Diabetes Association. State Insulin Copay Caps. Accessed 23 August 2024. Available from https://diabetes.org/tools-resources/affordable-insulin/state-insulin-copay-caps
202. Suran M. All 3 major insulin manufacturers are cutting their prices-here's what the news means for patients with diabetes. JAMA 2023; 329:1337–1339
203. Herges JR, Neumiller JJ, McCoy RG. Easing the financial burden of diabetes management: a guide for patients and primary care clinicians. Clin Diabetes 2021;39:427–436
204. U.S. Food & Drug Administration. FDA Drug Shortages. Current and Resolved Drug Shortages and Discontinuations Reported to FDA. Accessed 19 August 2024. Available from https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm
205. U.S. Food & Drug Administration. Drug Compounding and Drug Shortages. Accessed 6 June 2024. Available from https://www.fda.gov/drugs/human-drug-compounding/drug-compounding-and-drug-shortages
206. Ashraf AR, Mackey TK, Schmidt J, et al. Safety and risk assessment of no-prescription online semaglutide purchases. JAMA Netw Open 2024;7:e2428280
207. U.S. Food & Drug Administration. FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products. Accessed 29 July 2024. Available from https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded
208. Lambson JE, Flegal SC, Johnson AR. Administration errors of compounded semaglutide reported to a poison control center-case series. J Am Pharm Assoc 2023;63:1643–1645
209. U.S. Food & Drug Administration. FDA warns consumers not to use counterfeit Ozempic (semaglutide) found in U.S. drug supply chain. Accessed 18 January 2024. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-use-counterfeit-ozempic-semaglutide-found-us-drug-supply-chain
210. Neumiller JJ, Bajaj M, Bannuru RR, et al. Compounded GLP-1 and dual GIP/GLP-1 receptor agonists: a statement from the American Diabetes Association. Diabetes Care. 2 December 2024 [Epub ahead of print]. DOI: 10.2337/dci24-0091
211. Whitley HP, Trujillo JM, Neumiller JJ. Special report: potential strategies for addressing GLP-1 and dual GLP-1/GIP receptor agonist shortages. Clin Diabetes 2023;41:467–473
212. Urva S, Coskun T, Loghin C, et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists. Diabetes Obes Metab 2020;22:1886–1891
213. Skelley JW, Swearengin K, York AL, Glover LH. The impact of tirzepatide and glucagon-like peptide 1 receptor agonists on oral hormonal contraception. J Am Pharm Assoc 2024;64: 204–211 e204
214. National Library of Medicine. National Center for Biotechnology Information. ClinicalTrials.gov. A study of the effect of tirzepatide on how the body handles birth control pills in healthy female participants (NCT04172987). Accessed 12 June 2024. Available from https://clinicaltrials.gov/study/NCT04172987
215. U.S. Food & Drug Administration. Tirzepatide prescribing information. Accessed 12 June 2024. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf
216. Byun DJ, Braunstein R, Flynn J, et al. Immune checkpoint inhibitor-associated diabetes: a single-institution experience. Diabetes Care 2020;43: 3106–3109
217. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol 2018;4:173–182
218. Liu J, Zhou H, Zhang Y, et al. Reporting of immune checkpoint inhibitor therapy-associated diabetes, 2015-2019. Diabetes Care 2020;43: e79–e80
219. Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-kinase, growth disorders, and cancer. N Engl J Med 2018;379:2052–2062
220. André F, Ciruelos E, Rubovszky G, et al.; SOLAR-1 Study Group. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929–1940
221. André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol 2021;32:208–217
222. Rugo HS, André F, Yamashita T, et al. Time course and management of key adverse events

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during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. Ann Oncol 2020;31:1001–1010
223. Gallagher EJ, Moore H, Lacouture ME, et al. Managing hyperglycemia and rash associated with alpelisib: expert consensus recommendations using the Delphi technique. NPJ Breast Cancer 2024;10:12
224. Goncalves MD, Farooki A. Management of phosphatidylinositol-3-kinase inhibitor-associated hyperglycemia. Integr Cancer Ther 2022;21: 15347354211073163
225. Cheung Y-MM, McDonnell M, Hamnvik O-PR. A targeted approach to phosphoinositide-3-kinase/Akt/mammalian target of rapamycin-induced hyperglycemia. Curr Probl Cancer 2022; 46:100776
226. Ode KL, Ballman M, Battezzati A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2022;23:1212–1228
227. Lo C, Toyama T, Oshima M, et al. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. Cochrane Database Syst Rev 2020; 8:CD009966
228. Munoz Pena JM, Cusi K. Posttransplant diabetes mellitus: recent developments in pharmacological management of hyperglycemia. J Clin Endocrinol Metab 2023;109:e1–e11
229. Ram E, Lavee J, Tenenbaum A, et al. Metformin therapy in patients with diabetes mellitus is associated with a reduced risk of vasculopathy and cardiovascular mortality after heart transplantation. Cardiovasc Diabetol 2019; 18:118
230. Vest LS, Koraishy FM, Zhang Z, et al. Metformin use in the first year after kidney transplant, correlates, and associated outcomes in diabetic transplant recipients: a retrospective analysis of integrated registry and pharmacy claims data. Clin Transplant 2018;32:e13302
231. Thangavelu T, Lyden E, Shivaswamy V. A retrospective study of glucagon-like peptide 1 receptor agonists for the management of diabetes after transplantation. Diabetes Ther 2020;11:987–994
232. Kukla A, Hill J, Merzkani M, et al. The use of GLP1R agonists for the treatment of type 2 diabetes in kidney transplant recipients. Transplant Direct 2020;6:e524
233. Singh P, Pesavento TE, Washburn K, Walsh D, Meng S. Largest single-centre experience of dulaglutide for management of diabetes mellitus in solid organ transplant recipients. Diabetes Obes Metab 2019;21:1061–1065
234. Greeley SAW, Polak M, Njølstad PR, et al. ISPAD Clinical Practice Consensus Guidelines 2022: the diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2022;23:1188–1211
235. Christensen AS, Hædersdal S, Støy J, et al. Efficacy and safety of glimepiride with or without linagliptin treatment in patients with HNF1A diabetes (maturity-onset diabetes of the young type 3): a randomized, double-blinded, placebo-controlled, crossover trial (GLIMLINA). Diabetes Care 2020;43:2025–2033
236. Umpierrez GE, Davis GM, ElSayed NA, et al. Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care 2024;47:1257–1275
237. Wolfsdorf JI, Ratner RE. SGLT inhibitors for type 1 diabetes: proceed with extreme caution. Diabetes Care 2019;42:991–993
238. Colacci M, Fralick J, Odutayo A, Fralick M. Sodium-glucose cotransporter-2 inhibitors and risk of diabetic ketoacidosis among adults with type 2 diabetes: a systematic review and meta-analysis. Can J Diabetes 2022;46:10–15
239. Bonora BM, Avogaro A, Fadini GP. Sodium-glucose co-transporter-2 inhibitors and diabetic ketoacidosis: an updated review of the literature. Diabetes Obes Metab 2018;20:25–33
240. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. Diabetes Metab Res Rev 2017;33:10.1002/dmrr.2924
241. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Obes Metab 2021;23:2116–2124
242. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701

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